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UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA

AMARIN PHARMA, INC. and AMARIN PHARMACEUTICALS IRELAND LIMITED,

Plaintiffs,

v.

HIKMA PHARMACEUTICALS USA INC., *et al.*,

Defendants.

CASE NO.: 2:16-cv-02525-MMD-NJK

(Consolidated with 2:16-cv-02562-MMD-NJK)

PLAINTIFFS' PRETRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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I. JURISDICTION AND VENUE

1. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) because it arises under the Patent Laws of the United States, 35 U.S.C. § 100, et seq.

2. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

3. For purposes of this action only, no party contests personal jurisdiction or venue in this Court.

II. PARTIES AND PATENT OWNERSHIP

A. The Parties

4. Plaintiff Amarin Pharma, Inc. is a company organized and existing under the laws of Delaware with its principal place of business at 440 Route 22, Bridgewater, NJ 08807. Joint Stipulated Facts ¶ 2 (ECF No. 324).

5. Plaintiff Amarin Pharmaceuticals Ireland Limited is a company incorporated under the laws of Ireland with registered offices at 88 Harcourt Street, Dublin 2, Dublin, Ireland. Joint Stipulated Facts ¶ 3 (ECF No. 324).

6. Defendant Hikma Pharmaceuticals USA Inc. is a company organized and existing under the laws of Delaware with its principal place of business at 246 Industrial Way West, Eatontown, NJ 07724. Joint Stipulated Facts ¶ 4 (ECF No. 324).

7. Defendant Hikma Pharmaceuticals International Limited is a company incorporated under the laws of the United Kingdom with registered offices at 1 New Burlington Place, London, England W1S 2HR. Joint Stipulated Facts ¶ 5 (ECF No. 324).

8. Defendant Dr. Reddy's Laboratories, Inc. is a company organized and existing under the laws of New Jersey with its principal place of business at 107 College Road East, Princeton, NJ 08540. Joint Stipulated Facts ¶ 6 (ECF No. 324).

9. Defendant Dr. Reddy's Laboratories, Ltd. is an Indian public limited liability company organized and existing under the laws of India and having a principal place of business

at 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Andhra Pradesh 500 034, India. Joint Stipulated Facts ¶ 7 (ECF No. 324).

B. The Asserted Patents

10. Amarin asserts the following patents: U.S. Patent No. 8,293,728 ("the '728 Patent"), U.S. Patent No. 8,318,715 ("the '715 Patent"), U.S. Patent No. 8,357,677 ("the '677 Patent"), U.S. Patent No. 8,367,652 ("the '652 Patent"), U.S. Patent No. 8,431,560 ("the '560 Patent"), and U.S. Patent No. 8,518,929 ("the '929 Patent") (collectively, the "Asserted Patents"). PX 21, PX 22, PX 25, PX 26, PX 30, PX 31.

11. Each of the Asserted Patents is entitled "METHODS OF TREATING HYPERTRIGLYCERIDEMIA."

12. The U.S. Applications that ultimately issued as the Asserted Patents are continuations of U.S. Application No. 12/702,889, filed on February 9, 2010, which ultimately issued as U.S. Patent No. 8,293,727 ("the '727 Patent").

13. The Asserted Patents further claim priority to U.S. Provisional Application No. 61/151,291, filed on February 10, 2009, and U.S. Provisional Application No. 61/173,755, filed on April 29, 2009.

14. Mehar Manku, Ian Osterloh, Pierre Wicker, Rene Braeckman, and Paresh Soni are named as inventors of the Asserted Patents.

15. Pursuant to 21 U.S.C. § 355(b)(1), the Asserted Patents are listed in the Orange Book—a Food and Drug Administration ("FDA") publication formally known as *Approved Drug Products with Therapeutic Equivalence Evaluations*—in connection with NDA No. 202057.

C. The Asserted Claims

16. Amarin has asserted Claims 1 and 16 of the '728 Patent.

17. Amarin has asserted Claim 14 of the '715 Patent.

18. Amarin has asserted Claims 1 and 8 of the '677 Patent.

19. Amarin has asserted Claim 1 of the '652 Patent.

20. Amarin has asserted Claims 4 and 17 of the '560 Patent.

21. Amarin has asserted Claims 1 and 5 of the '929 Patent.

22. These claims are referred to collectively herein as the "Asserted Claims."

D. Priority Date

23. The Asserted Claims are entitled to a priority date of no later than March 2008, and references published after March 2008 are not prior art.

24. The inventors of the Asserted Patents conceived of the inventions disclosed in the Asserted Claims by March 25, 2008. *See, e.g.*, PX 472, Email from D. Doogan to M. Manku et al.; PX 474, Email from M. Manku to D. Cunningham et al. (Mar. 13, 2008); PX 475, Email from M. Manku to A. Cooke et al. (Mar. 16, 2008); PX 476, Email from M. Manku to D. Cunningham et al. (Mar. 25, 2008), PX 1132, Email from M. Manku to D. Cunningham et al. (Mar. 24, 2008); *see also, e.g.*, M. Manku Dep. Tr. at 84:5–85:8; 89:6–93:12; 131:15–19; 132:1–2; 132:4; 132:6–17; 145:8–19; 153:18–154:4.

25. The claims were diligently reduced to practice, including through the submission to FDA of information to permit the carrying out of the MARINE clinical trial confirming the claimed inventions and the filing of a provisional patent application on February 10, 2009. *See, e.g.*, PX 482, Letter from David Zuchero to Mary Parks (May 9, 2008); PX 481, Letter from David Zuchero to Mary Parks (June 16, 2008); PX 470, Email from I. Osterloh to R. Braeckman et al. (Dec. 15, 2008).

26. Neither side's experts disputed the March 2008 priority date. To the contrary, Amarin's experts and Defendants' experts assumed a March 2008 priority date in forming their opinions in this case.

E. Person of Ordinary Skill in the Art

27. The Asserted Claims and the prior art are evaluated at the time of the invention from the standpoint of a person of ordinary skill in the art ("POSA"). A person of ordinary skill in the art is a hypothetical person who is presumed to have access to, and be aware of, all of the relevant prior art at the time of the invention. Factors that may be considered in determining the

level of ordinary skill in the art may include: (1) type of problems encountered in the art, (2) prior art solutions to those problems, (3) rapidity with which innovations are made, (4) sophistication of the technology, and (5) educational level of active workers in the field.

28. The person of ordinary skill in the art in this case world be (1) a clinician with an M.D., or D.O. and at least 2 to 3 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia (*i.e.*, TG levels of at least 500 mg/dl), or (2), alternatively, a clinician, such as a nurse practitioner or physician's assistant, with 3 to 5 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia.[1]

III. FACT WITNESSES TO BE PRESENTED AT TRIAL

A. Amarin's Witnesses

1. Steven Ketchum, Ph.D.

29. Dr. Ketchum is the President of Research & Development and a Senior Vice President at Amarin Pharma, Inc.

30. Dr. Ketchum has a Ph.D. in Pharmacology from University College London.

31. Dr. Ketchum has over 20 years of experience in late-stage drug development and clinical regulatory strategy, having led the filings of successful NDAs and sNDAs while serving in regulatory affairs and research & development roles at several pharmaceutical companies.

32. As head of Research & Development at Amarin, Dr. Ketchum oversees the scientific disciplines that flow into the drug development and registration process, including Amarin's clinical, pharmaceutical development, quality assurance, and regulatory affairs teams.

33. Since joining Amarin in February 2012, Dr. Ketchum has been involved in all facets of the VASCEPA® clinical and regulatory program, from negotiating VASCEPA®'s first FDA approval in July 2012 to its newest FDA-approved indication in December 2019.

[1] Defendants propose a different definition for the person of ordinary skill in the art. But both sides agree that the infringement and validity analyses do not change regardless of which definition is used.

2. Rebecca Juliano, Ph.D.

34. Dr. Juliano is the Senior Vice President of Clinical Research & Development at Amarin Pharma, Inc.

35. Dr. Juliano has a Ph.D. in Nutritional Biochemistry from Columbia University, where her graduate research focused on lipid science, including fatty acids and cholesterol. After completing her Ph.D., Dr. Juliano continued her lipid-science research as postdoctoral fellow of the American Heart Association at Weill Cornell Medical Center.

36. Since joining Amarin as the Director of Clinical Research & Development, Dr. Juliano has played a key role in the REDUCE-IT clinical study, overseeing the operations and clinical study teams and providing critical scientific support for Amarin's sNDA for a new indication based on the results of the REDUCE-IT study.

3. Aaron Berg

37. Mr. Berg has over 25 years of life science industry experience and joined Amarin in November 2012 as Vice President, Marketing and Managed Care. He has played a leading role in U.S. prescription and related revenue growth of Amarin's lead product, VASCEPA®.

38. Mr. Berg was promoted to Senior Vice President, Marketing and Sales in February 2014, and to the position of Senior Vice President and Chief Commercial Officer in April 2018. He is responsible for ensuring continued commercial growth for VASCEPA® and successful expanded promotion of VASCEPA® based on the positive results of Amarin's landmark REDUCE-IT cardiovascular outcomes trial.

39. Before joining Amarin, Mr. Berg served as President and Chief Executive Officer for Essentialis, Inc., a development stage pharmaceutical company where he led the company's work on triglyceride management. Prior to joining Essentialis, Mr. Berg served as Vice President of Marketing and Sales at Kos Pharmaceuticals, where he was instrumental in driving annual revenues approaching $1 billion and was there until the acquisition of the company by Abbott Laboratories in December 2006 for $3.7 billion. Mr. Berg began his pharmaceutical

industry career as a sales representative with Bristol-Myers Squibb, followed by various commercial positions with Schering-Plough and GlaxoSmithKline.

B. Defendants' Witnesses

40. Amarin does not expect Defendants to call any fact witnesses at trial.

IV. EXPERT WITNESSES TO BE PRESENTED AT TRIAL ON THE ISSUE OF INFRINGEMENT

A. Amarin's Witnesses

1. Matthew Budoff, M.D.

41. Dr. Budoff is an expert in the clinical treatment of patients with lipid disorders, including severe hypertriglyceridemia, and an expert in cardiology. Dr. Budoff will testify regarding the prescribing practices of clinicians, like himself, who prescribe VASCEPA® to patients with severe hypertriglyceridemia, in accordance with the VASCEPA® label. In particular, Dr. Budoff will testify that clinicians read the VASCEPA® label, and will read Defendants' proposed labels as encouraging, recommending, promoting, or suggesting that clinicians administer VASCEPA®, or Defendants' ANDA Products, in a manner that infringes the Asserted Claims.

42. Dr. Budoff has practiced in the field of preventive cardiology for over twenty years. He maintains an active clinical practice where he treats approximately 200 patients per month, many of whom have elevated triglycerides and are at increased risk for cardiovascular events. He also directly supervises cardiology fellows in their treatment of several hundred patients per week. PX 1161 at 000001–02, Curriculum Vitae of Matthew Budoff, M.D.

43. Dr. Budoff is currently the Program Director at the Lundquist Institute for Biomedical Innovation, affiliated with the David Geffen School of Medicine at the University of California, Los Angeles (UCLA) and Harbor UCLA Medical Center. *Id.* at 000001. In addition to serving as program director, Dr. Budoff is employed as a researcher and Professor of Medicine. *Id.* at 000001–02.

44. As a Professor of Medicine, Dr. Budoff instructs and supervises current medical students, interns, residents, and cardiology fellows. This includes teaching courses, giving lectures, and supervising the treatment of patients.

45. Outside of his obligations as a Professor of Medicine, Dr. Budoff regularly lectures practicing clinicians (physicians, physician assistants, nurse practitioners, nurses, etc.) at large symposia and national and international meetings on the treatment of various aspects of preventive cardiovascular health, including lipid abnormalities, cardiac imaging, and heart disease risk.

46. In his capacity as a researcher, Dr. Budoff performs and supervises clinical studies, having supervised over 100 clinical studies as a principal investigator. As the principal investigator of a clinical study, Dr. Budoff is responsible for all aspects of the study including conception (writing the grant), design of the study (how many patients, how to follow up, what the end points will be), execution of the study, and publication of study results. For example, Dr. Budoff was an investigator on two studies involving VASCEPA® as well as many others involving other lipid lowering agents. *See, e.g.*, *id.* at 000069, 000082, 000135, 000150.

47. Dr. Budoff has received significant recognition for his work. *Id*. at 000003–06. He was appointed to serve as the Endowed Chair of Preventive Cardiology at the Lundquist Institute for Biomedical Innovation and has previously been appointed to positions including Foundation Board Member of the American College of Cardiology, Chair of the Annual Scientific Meeting Committee, and the president of societies including the Society of Cardiovascular Computed Tomography and the Society of Atherosclerosis Imaging and Prevention. *Id.* at 000001–03. Most recently, Dr. Budoff was named to the World's Most Influential Scientific Researchers in 2018 and 2019, America's Most Honored Professionals in 2019, and was inducted into the World Academy of Sciences in 2019. *Id.* at 000004.

2. Carl Peck, M.D.

48. Dr. Peck is an expert in FDA's review processes and regulatory requirements for new and generic pharmaceutical drugs. Dr. Peck will testify regarding the FDA's requirements

for prescription drug labeling and the role that labeling plays in prescribing decisions. Dr. Peck will also testify that, consistent with FDA regulations and guidance, Defendants' proposed labeling will encourage, recommend, promote, or suggest administration of Defendants' ANDA Products in a manner that infringes specific limitations of the Asserted Claims.

49. Dr. Peck is a physician scientist with five decades of combined experience in internal medicine, clinical pharmacology, clinical trial design and analysis, and the development and regulation of pharmaceutical products. Dr. Peck is board certified in internal medicine and clinical pharmacology, and he held several medical, research, and teaching posts over a twenty-year career in the U.S. Army Medical Corps. PX 1109 at 000002–04, Curriculum Vitae of Carl C. Peck, M.D. From 1987 to 1993, Dr. Peck served as the Director of the Center for Drug Evaluation and Research, the FDA center responsible for evaluating and approving all new and generic drugs for use in humans. *Id.* at 000004.

50. Since leaving government service, Dr. Peck has directed the Center for Drug Development Science at Georgetown University and the University of California, San Francisco, and continued researching and teaching in the fields of drug development and regulation. As Founder and Chairman of NDA Partners, LLC, Dr. Peck also routinely consults with clients on clinical trial design and analysis and FDA's regulatory requirements for new drugs. *Id.* at 000002, 000004.

B. Defendants' Witnesses

1. Jonathan I. Sheinberg, M.D.

51. Dr. Sheinberg is a board-certified cardiologist with a clinical cardiology practice at the Baylor Scott & White Health Medical Center in Austin, Texas. Amarin expects that he will testify concerning Defendants' alleged non-infringement of the Asserted Patents.

2. Peter R. Mathers

52. Mr. Mathers is a partner in the Washington, D.C. law firm of Kleinfeld, Kaplan and Becker LLP, where he practices food and drug law. Amarin expects that he will testify concerning FDA regulatory requirements for prescription drug labeling.

V. EXPERT WITNESSES TO BE PRESENTED AT TRIAL ON THE ISSUES OF NONOBVIOUSNESS AND OBJECTIVE INDICIA OF NONOBVIOUSNESS

A. Amarin's Witnesses

1. Firhaad Ismail, M.D., F.A.C.E

53. Dr. Ismail is currently a practicing clinician based in Las Vegas, Nevada. He is board certified in endocrinology and metabolism and is a fellow of the American College of Endocrinology. PX 1049 at 000002, Curriculum Vitae of Firhaad Ismail, M.D., F.A.C.E. Dr. Ismail will testify that VASCEPA® met the need for a treatment for diabetic patients with severe hypertriglyceridemia that does not raise LDL-C and that decreases apoB. Dr. Ismail will also testify that VASCEPA® unexpectedly met the need to lower cardiovascular disease risk in these diabetic patients.

54. Dr. Ismail earned his Medical Degree with Honors in 1974 from the University of Cape Town in South Africa. In 1983, he earned a Research Doctorate (equivalent to a Ph.D.) in Protein Biochemistry also from the University of Cape Town. He also became a Member of the Royal College of Physicians (United Kingdom) in 1978. *Id.* at 000002, 000004.

55. Dr. Ismail served as the Medical Director and Board Member for the Cholesterol Treatment Center at the Albert Einstein Medical Center. Later, after moving to Nevada, he served as the Medical Director for the Diabetes Center of Excellence at Sunrise Hospital in Las Vegas and then as the Chief of the Division of Endocrinology at Sunrise Hospital from 2007–2013. *Id.* at 000003.

56. In his current private practice, Dr. Ismail sees approximately 65–70 patients per week with the majority (75% or more) being diabetic. Most of his diabetic patients have type 2 diabetes, and the vast majority have elevated triglyceride levels. His patients are usually referred to him by primary care physicians and sub-specialists; the majority of his patients are referred to him by cardiologists. As part of these referrals, he is frequently requested to see patients with dyslipidemia, including severe hypertriglyceridemia. He therefore consistently sees patients with severe hypertriglyceridemia.

2. Peter Toth, M.D., Ph.D.

57. Dr. Toth is an expert in the clinical treatment of patients with lipid disorders, including severe hypertriglyceridemia, and an expert in cardiology. PX 1172, Curriculum Vitae of Peter Toth (Nov. 15, 2019). Dr. Toth will testify regarding the non-obviousness of the Asserted Claims. In particular, Dr. Toth will testify that VASCEPA®, and the Asserted Claims whose use VASCEPA® embodies, would not have been obvious to a person of ordinary skill in the art at the time of the invention. He will further testify that several objective indicia support the non-obviousness of the Asserted Claims.

58. Dr. Toth has practiced in the fields of family medicine, lipidology, and preventive cardiology for over twenty years. He maintains an active clinical practice where he treats over 400 patients per month, many of whom have elevated triglycerides and are at increased risk for cardiovascular events. *Id.* at 000001–03, Curriculum Vitae of Peter Toth, M.D., Ph.D.

59. Dr. Toth is currently the Director of Preventive Cardiology at the CGH Medical Center in Sterling, Illinois. In his capacity as Director of Preventive Cardiology, Dr. Toth makes recommendations based on developments in the field of cardiovascular disease prevention that guides the practice of other practicing physicians in the hospital. *See id.* at 000001, 000003.

60. Dr. Toth also holds positions on the faculty at medical schools, including University of Illinois School of Medicine, Michigan State University College of Osteopathic Medicine, and Johns Hopkins School of Medicine. In his faculty positions, Dr. Toth instructs and supervises current medical students during their clinical rotations, lectures at Continuing Medical Education symposia, and collaborates on research concerning cardiovascular medicines. *Id.* at 000001.

61. Dr. Toth also holds leadership positions in various professional organizations, including as President-elect of the American Society of Preventive Cardiology, past-President of the National Lipid Association, past-President of the Midwest Lipid Association, and past-President of the American Board of Clinical Lipidology. As the President of the American

Board of Clinical Lipidology, Dr. Toth oversaw the board certification process for physicians in the field of clinical lipidology. *Id.* at 000001–07.

62. In his capacity as a researcher, Dr. Toth performs and supervises clinical studies as a primary investigator and performs analytical research into data from clinical trials. *Id.* 000007–08.

63. Dr. Toth has authored or co-authored over 700 publications, including 375 research papers, 75 book chapters, and over 275 abstracts, the vast majority of which concern the fields of lipidology and cardiovascular disease prevention. *Id.* at 000011–91.

3. R. Preston Mason, Ph.D.

64. Dr. Mason has been a member of the Cardiovascular Division at the Harvard Medical School-affiliated Brigham and Women's Hospital in Boston, Massachusetts, since 2002. PX 1057 at 000002, Curriculum Vitae of R. Preston Mason, Ph.D. He is also President of Elucida Research LLC, a private biotechnology firm, in Beverly, Massachusetts, that he founded in 2001. *Id.* He conducts research and teaches in the areas of cardiovascular pharmacology, atherosclerosis, and lipid biochemistry including endothelial dysfunction, vascular inflammation, and lipid oxidation. Dr. Mason will testify that several lines of emerging scientific evidence suggest that EPA achieves its dramatic and unexpected reduction in cardiovascular risk through mechanisms including membrane stabilization, endothelial function improvement, plaque stabilization and regression, and anti-inflammatory effect. Dr. Mason will also testify that, through these mechanisms, patients with TG levels of at least 500 mg/dl would likely experience the dramatic cardiovascular risk reduction observed in REDUCE-IT.

65. Dr. Mason earned a Ph.D. in Biophysics and Cell Biology in 1989 from the University of Connecticut School of Medicine. *Id.* After earning his Ph.D., he completed two American Heart Association postdoctoral fellowships in 1990 and 1991 and the John A. Hartford Foundation research fellowship in 1992 at the University of Connecticut School of Medicine. *Id.*

66. Dr. Mason has served on numerous grant review committees for the National Institutes of Health and other organizations. *Id.* at 000003. He has been the recipient of many

awards and patents for his research in cardiovascular pharmacology, including an honorary doctorate in science. *Id.*

67. Dr. Mason has authored or coauthored more than 200 book chapters, abstracts, and articles in peer-reviewed journals, focusing on the areas of cardiovascular pharmacology, atherosclerosis, and lipid biochemistry including endothelial dysfunction, vascular inflammation, and lipid oxidation. *Id.* at 000014–25. He is a frequently invited speaker at national and international conferences on these topics. *Id.* at 000004–13.

4. Sean Nicholson, Ph.D.

68. Dr. Nicholson is a Professor in the Department of Policy Analysis and Management, the Director of the Sloan Program in Health Administration at Cornell University, and a Research Associate at the National Bureau of Economic Research. PX 1098 at 000002, Curriculum Vitae of Sean Nicholson, Ph.D. Prior to joining Cornell, he served as an Assistant Professor in Healthcare Systems at the Wharton School of the University of Pennsylvania. *Id.* He has a Ph.D. in Economics from the University of Wisconsin-Madison and an A.B. in Economics from Dartmouth College. *Id.* His research and teaching specialty is the economics of healthcare. Dr. Nicholson will testify that VASCEPA® is a commercial success and that there is a nexus between the success and the claimed invention.

69. In his academic career, Dr. Nicholson has researched the economics of the healthcare industry, with an emphasis on the pharmaceutical and biotechnology sectors. In this field of study, he has published articles in leading academic journals and presented his research at academic conferences. *Id.* 000002–12. He co-edited *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, published in 2012. *Id.* at 000004. In addition, he has served as a principal investigator on research projects sponsored by the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, the Robert Wood Johnson Foundation, and by leading biopharmaceutical companies. *Id.* 000007–09. He has also consulted and provided executive education to several biopharmaceutical companies. *Id.*

70. Dr. Nicholson's research projects have included identifying what types of firms are most effective at developing drugs, assessing risk in the healthcare industry, and determining the value of new medical technologies. He has done extensive research on the risks and uncertainties facing pharmaceutical companies. He has also conducted research and offered expert testimony in litigation involving the pharmaceutical industry.

B. Defendants' Witnesses

1. Jay W. Heinecke, M.D.

71. Dr. Heinecke is a Professor of Medicine at the University of Washington School of Medicine at the UW Medical Center in Seattle, Washington. Amarin expects that he will testify concerning the alleged obviousness of the Asserted Patents.

2. Edward A. Fisher, M.D.

72. Dr. Fisher is a Professor of Cardiovascular Medicine, and Professor in the Departments of Medicine, Pediatrics and Cell Biology at the N.Y.U. School of Medicine. Amarin expects that he will testify concerning the alleged obviousness of the Asserted Patents.

3. Ivan T. Hofmann

73. Mr. Hofmann is a Vice President and Managing Director at Gleason IP, an economic, accounting, and financial consulting firm. Amarin expects that he will testify concerning the issues of commercial success and nexus with respect to the Asserted Patents.

VI. WITNESSES THAT MAY TESTIFY BY DEPOSITION DESIGNATIONS

A. Amarin's Deposition Designations

74. Amarin may offer excerpts from the depositions of the following witnesses, who are not expected to testify live at trial.

1. Ian Osterloh, M.D.

75. Dr. Osterloh is one of the named inventors of the Asserted Patents. He graduated from medical school in 1982, and obtained membership into the Royal College of Physicians in 1985. In 1986, Dr. Osterloh began a more than two-decade career in clinical research and

development at Pfizer in the United Kingdom. In 2007, Dr. Osterloh joined Amarin as a consultant on the severe hypertriglyceridemia clinical research and development program.

2. Mehar Manku, Ph.D.

76. Dr. Manku is one of the named inventors of the Asserted Patents. He received his Ph.D. from Newcastle University in 1975. Thereafter, Dr. Manku began a more than four-decade career researching and studying fatty acids in animal models and humans, with particular focus on the metabolism of ethyl-eicosapentaenoic acid in the body. During his career, Dr. Manku held senior research positions with a number of companies focused on the development of fatty acids as medicines. Beginning in 2007, Dr. Manku served as Amarin's Vice President of Research and Development. Throughout his career at Amarin, Dr. Manku played a central role in the development of VASCEPA®.

3. Howard S. Weintraub, M.D.

77. Dr. Weintraub is the Clinical Director of the Center for the Prevention of Cardiovascular Disease at New York University Medical Center. Dr. Weintraub's research focuses on cholesterol, blood sugar, and cardiovascular disease, and he is the author or co-author of more than 30 scientific and technical papers. As a practicing cardiologist, Dr. Weintraub treats thousands of patients for lipid disorders annually. Dr. Weintraub submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

4. Ronald H. Wharton, M.D.

78. Dr. Wharton is an Assistant Professor of Medicine (Cardiology) at the Albert Einstein College of Medicine, and an attending cardiologist at Montefiore Medical Center, in Bronx, New York. Defendants submitted opinion testimony from Dr. Wharton during the claim construction proceedings.

5. Jerald Andry, Pharm.D.

79. Jerald Andry is the Senior Director of Drug Regulatory Affairs and Medical Affairs at Hikma Pharmaceuticals USA Inc.

6. Andrea Cady, Ph.D.

80. Andrea Cady is the Senior Director of Product Development at Hikma Pharmaceuticals USA Inc.

7. Jaya Ayyagari

81. Jaya Ayyagari is the Director of Regulatory Affairs at Dr. Reddy's Laboratories, Inc.

8. Anuj Srivastava, Ph.D.

82. At the time of his deposition, Anuj Srivastava was the Senior Director of Strategic Portfolio & Business Development at Dr. Reddy's Laboratories, Inc.

B. Defendants' Deposition Designations

83. Amarin expects that Defendants may seek to offer excerpts from the depositions of the following additional witnesses, who are not expected to testify live at trial.

1. Michael Miller, M.D.

84. Dr. Miller is Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine. Dr. Miller has served as the Director of the Center for Preventive Cardiology at the University of Maryland Medical Center since 1991. Amarin asked Dr. Miller to offer his expert opinion during claim construction regarding how a person of ordinary skill in the art would understand certain terms in the Asserted Claims.

2. Harold E. Bays, M.D.

85. Dr. Bays is the Medical Director and President of Louisville Metabolic and Atherosclerosis Research Center. Dr. Bays received his medical degree and completed his internship, residency, and fellowship in endocrinology and metabolism at the University of Louisville School of Medicine. Over the course of his career, Dr. Bays has been an investigator in hundreds of clinical trials for cholesterol and lipid disorders, obesity, diabetes mellitus, hypertension, osteoporosis, and other metabolic and hormonal disorders. Dr. Bays submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

3. Philip Lavin, Ph.D.

86. Dr. Lavin has a Ph.D. in Applied Mathematics from Brown University. Dr. Lavin is self-employed through Lavin Consulting LLC as a biostatistics consultant. Dr. Lavin submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

VII. BACKGROUND OF THE INVENTION

A. Triglycerides

87. The Asserted Claims are directed to methods of treating patients with severe hypertriglyceridemia, or very-high triglycerides ("VHTGs"), *i.e.*, at least 500 mg/dl.

88. Triglycerides ("TGs") are a type of fat found in blood, and belong to a class of molecules called lipids. TGs serve the critical role of distributing energy to tissues in the body. But TG levels can reach a point at which they become abnormally high and pose serious health risks.

89. Another type of lipid found in the blood is cholesterol. Unlike TGs, cholesterol is not a source of energy. Instead, cholesterol is a building block for some hormones. But, as with TGs, certain kinds of lipoproteins carrying cholesterol in blood can pose serious health risks if present in the body in levels that are too high.

B. Lipoproteins

90. Lipids including TGs and cholesterol do not dissolve in plasma (the water part of the blood). As a result, TGs and cholesterol cannot be transported through the bloodstream on their own. They must instead move through the bloodstream as part of biochemical units called lipoproteins.

91. Lipoproteins are "large, mostly spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat-soluble vitamins) though body fluids (plasma, interstitial fluid, and lymph) to and from other tissues." PX 891 at 000006, Rader et al., *Disorders of Lipoprotein Metabolism, in Harrison's Principles of Internal Medicine* 2286 (Dennis L. Kasper et al. eds., 16th ed., 2005) at AMRN-PEXP-0001757.

92. Lipoproteins consist of two primary constituents: lipids and proteins (known as apolipoproteins or apoproteins). The lipid constituents of lipoproteins are TGs, cholesterol and cholesterol esters, and phospholipids. The protein component in lipoproteins provides a scaffolding upon which lipids can be assimilated and they provide structural stability.

93. Lipoproteins contain a core containing TGs and cholesterol esters, and a surrounding surface layer consisting of phospholipids and apoproteins. PX 921 at 000005, Mahley et al., *Drug Therapy for Hypercholesterolemia and Dyslipidemia, in The Pharmacological Basis of Therapeutics* 971 (Goodman & Gilman et al. eds., 10th ed. 2001) ("Mahley") at AMRN00290362. The core consists of the most hydrophobic (*i.e.*, water-insoluble) components, while the surface components are hydrophilic, and hence water soluble. These surface components sequester the hydrophobic core from water in the blood, and thereby allow for transport of lipids through the bloodstream.

94. There are different types of lipoproteins, which vary in terms of their composition and density. The density of a lipoprotein is determined by the amount of lipid and protein per particle. The five major classes of lipoproteins, as understood as of March 2008, were: very low-density lipoproteins ("VLDL"), intermediate-density lipoproteins ("IDL"), low-density lipoproteins ("LDL"), chylomicrons, and high-density lipoproteins ("HDL"). PX 486 at 000003, Bays et al., *Prescription Omega-3 Fatty Acids and Their Lipid Effects: Physiologic Mechanisms of Action and Clinical Implications*, 6 Expert Rev. Cardiovascular Therapy 391 (2008) ("Bays 2008 I") at AMRN009920973 at Table 1; PX 877 at 000002, Ginsberg, *Lipoprotein Metabolism and its Relationship to Atherosclerosis*, 78 Med. Clinics N. Am. 1 (1994), AMRN-PEXP-001440, Table 1.

95. VLDL particles are predominantly composed of TGs, with a relatively small proportion of cholesterol. VLDL particles are synthesized in the liver, and then secreted in the bloodstream, where an enzyme called lipoprotein lipase strips away the TGs in VLDL particles, releasing them as free fatty acids that are oxidized and either used as an energy source by skeletal muscles and other tissues, or reassembled into TGs and stored as fat. In March 2008, it

was understood that VLDL particles constitute approximately 90% of the TG-containing lipoproteins. PX 924 at 000003–04, 000007, McKenney, *Dyslipidemias, Atherosclerosis, and Coronary Heart Disease, in Applied Therapeutics: The Clinical Use of Drugs* 13-1 (Mary Anne Koda-Kimble et al. eds., 8th ed. 2005) ("McKenney 2005") at AMRN00290755 & Figure 13-3.

96. As VLDL particles are depleted of TGs, the VLDL particles become smaller, denser particles called IDL. *See, e.g.*, *id.* at 000004, 000007; PX 921 at 000008, Mahley at AMRN00290365. These particles have a lower proportion of TGs than VLDL particles, and a relatively higher proportion of cholesterol. It was understood in March 2008 that while about half of IDL particles are removed from the blood by the liver, the other half undergo an additional conversion that further depletes the remaining TGs until the IDL particles become LDL particles, the end product of VLDL lipolysis. *Id*.

97. LDL particles are smaller and denser than IDL particles, with proportionally small amounts of TGs, and relatively large proportions of cholesterol. In fact, LDL is the most cholesterol rich lipoprotein. At the time of the invention, it was understood that approximately half of LDL particles that remained after conversion from IDL particles were removed from systemic circulation by the liver, while the other half were distributed throughout the peripheral tissues and arteries. PX 924 at 000004, 000006, McKenney 2005 at AMRN00290755, AMRN00290757.

98. As of March 2008, it was understood that VLDL, IDL, and LDL particles all had the potential to contribute to atherosclerosis, *i.e.*, the build-up of cholesterol in the arteries which can lead to heart disease. But LDL was the "most abundant and clearly evident atherogenic lipoprotein," PX 989 at 000022, American Heart Association, *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report*, 106 Circulation 3143 (2002) ("ATP-III") at AMRN00289936, and LDL-C, the cholesterol in LDL particles, was believed to make "the greatest contribution to the development of atherosclerosis." PX 924 at 000004, McKenney 2005 at AMRN00290755.

99. In March 2008, it was understood that LDL particles ordinarily accounted for approximately two-thirds of a patient's total blood cholesterol, *id.*; PX 921 at 000009, Mahley at AMRN00290366; PX 989 at 000022, ATP-III at AMRN00289936, and that "the probability that atherosclerosis will develop is directly related to the concentration of LDL-C in the systemic circulation and the length of time this level of exposure persists." PX 924 at 000006, McKenney 2005 at AMRN00290757.

100. After VLDL particles are produced in and secreted by the liver into the bloodstream, lipoprotein lipase breaks down TGs in the VLDL particles, releasing free fatty acids into circulation, where they can be further processed for energy by tissues throughout the body or repacked into TGs within adipose tissue. The smaller, denser, more cholesterol-rich remnants of the VLDL particles, called IDL particles, remain in the bloodstream until they are taken up by the liver or other peripheral tissues. Those IDL particles that are not removed from the blood by the liver undergo a further conversion into LDL particles, in which the remaining TGs are depleted.

101. A fourth class of lipoproteins is chylomicrons. As of March 2008, it was understood that, like VLDL particles, chylomicrons were also TG-rich—with relatively large proportions of TGs and relatively small proportions of cholesterol. *See, e.g.*, PX 414 at 000005, Bays 2008 I at AMRN03145056, Table 2; PX 989 at 000022, ATP-III at AMRN00289936. But unlike VLDL particles, chylomicrons are not synthesized in the liver; they are instead formed "in the intestine from dietary fat, and appear in the blood after a fat-containing meal." *Id.*.

102. Chylomicrons, VLDL, IDL, and LDL are all atherogenic, and all contain a single apolipoprotein B ("apoB") molecule (apoprotein B100, the scaffolding upon which VLDL is synthesized within hepatocytes and a constituent of all atherogenic lipoproteins). Therefore, measures of apoB represent the total burden of the main lipoprotein particles involved in the atherosclerotic process.

103. A fifth class of lipoproteins is HDL. In contrast to the other particles discussed above, HDL does not contain apoB. HDL is known to remove cholesterol from tissue and

transport it back to the liver for removal, in a process called reverse cholesterol transport. *See* PX 924 at 000006, McKenney 2005 at AMRN00290757. Because it was understood that HDL performs this function, and that certain cholesterol was associated with increased atherosclerotic risk, in 2008, high levels of HDL-C in the blood were thought to correlate with reduced atherosclerotic risk. *See* PX 921 at 000010, Mahley at AMRN00290367.

C. Hypertriglyceridemia

104. At the time of the invention, it was understood that TG levels in the blood could become elevated to levels exceeding 150 mg/dl, resulting in a lipid disorder known as hypertriglyceridemia. *See* PX 989 at 000190, ATP-III at AMRN00290104. Elevated TG levels were understood to be the result of an overproduction of lipoproteins in the liver or intestine, a reduction in the clearance of TGs from lipoproteins, or both. *Id*. at 000191.

105. Factors believed to contribute to hypertriglyceridemia included genetic factors; lifestyle factors (physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate intake (>60% of total energy), obesity); and secondary causes (including diabetes mellitus, chronic renal failure, nephrotic syndrome, Cushing's disease, lipodystrophy, pregnancy, and various drugs (corticosteroids, beta-blockers, retinoids, and oral estrogens)). *Id*. at 000190, Table VII.2-1; PX 925 at 000002, McKenney et al., *Role of Prescription Omega-3 Fatty Acids in the Treatment of Hypertriglyceridemia*, 27 Pharmacotherapy 715 (2007) ("McKenney 2007 I") at AMRN00290798.

106. Genetic conditions leading to chronic elevated TG levels were believed to increase production of the TG-rich lipoproteins VLDL and chylomicrons, or to decrease lipoprotein lipase activity, which meant reduced clearance of TG-rich lipoproteins from the bloodstream. *Id.*

107. Hypertriglyceridemia was understood to pose serious health risks, including cardiovascular disease and pancreatitis.

108. As of March 2008, doctors treating lipid disorders, including hypertriglyceridemia, relied on the third report of the National Cholesterol Education Program's

Adult Treatment Panel, the ATP-III, in treating hypertriglyceridemia. The ATP-III, an authoritative source of medical guidance, divided hypertriglyceridemia patients into three classes based on the levels of TGs in their blood—(1) borderline-high (150–199 mg/dl); (2) high (200–499 mg/dl); and (3) very high TGs (≥500 mg/dl). PX 989 at 000190, 000194, ATP-III at AMRN00290104, AMRN00290108.

109. Hypertriglyceridemic patients were, and are still today, categorized according to their fasting baseline triglyceride levels, determined by a blood test, where the blood must have been collected when the patient had fasted between 9–12 hours. *Id.* at 000091.

110. The ATP-III's differentiation among these classes of patients reflected the view that these groups faced different primary risks and had different treatment needs. For patients with borderline high or high TG levels (150-499 mg/dl), ATP-III's primary goal was to reduce the risk of coronary heart disease, whose underlying etiology is atherosclerosis. *Id*. at 000194. Because LDL particles were understood to be the most atherogenic lipoprotein, the chief concern for this class of patients was lowering LDL-C, which was the cholesterol associated with LDL. *Id*. at 000022, 000194. Lowering TG levels was a secondary priority for the borderline high or high TG patients. *Id*. at 000194.

D. Severe Hypertriglyceridemia

111. By contrast, the first and most urgent treatment priority for patients with severe hypertriglyceridemia (TGs ≥ 500 mg/dl), or very high triglycerides, was to address acute pancreatitis, with prevention of coronary heart disease constituting a second priority. *See id*. at 000194–95. Pancreatitis, which involves the inflammation of the pancreas, is a very painful condition that generally requires hospitalization and is potentially life threatening.

112. The widespread recognition that persons with very high TGs were a special population with distinct treatment needs was reflected in medical literature and FDA's regulatory review process, the latter of which recognized the distinction between patients with very high TGs and patients with borderline-high or high TGs in the grant of a discrete indication for patients having TG levels of at least 500 mg/dl. *See, e.g.*, PX 922 at 000003, LOVAZA®,

Physicians' Desk Reference (62d ed. 2008) ("LOVAZA® PDR") at AMRN00290593 ("INDICATIONS AND USAGE . . . Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels.").

113. Other references reflected the understanding that the very high TG group was a distinct class of patients with different treatment priorities than patients with borderline high or high TG levels. *See, e.g.*, PX 923 at 000010, McKenney, *Prescription Omega-3 Fatty Acids for the Treatment of Hypertriglyceridemia*, 64 Am. J. Health-System Pharmacy 595 (2007) ("McKenney 2007 II") at AMRN00290748 ("Very high triglycerides. While an increased risk of CHD may be present in patients with very high triglycerides (≥500 mg/dL [≥5.65 mmol/L]), the more urgent concern is the development of pancreatitis. . . . Triglyceride reduction is the treatment priority in these patients . . . . High triglycerides. . . . In these patients, NCEP ATP III recommends that a secondary goal, defined by non-HDL cholesterol, be established at 30 mg/dL above the patient's LDL cholesterol goal."); PX 414 at 000001, Bays 2008 I at AMRN03145052 ("For patients with very high TG levels (≥ 500 mg/dl . . . , the initial therapeutic goal is to . . . prevent pancreatitis, which is a potentially life-threatening complication of severe hypertriglyceridemia. The risk of pancreatitis is especially increased when TG levels are found to be above 1000 mg/dl (11.3 mmol/l).") (citation omitted).

114. It was also understood that genetic factors were more likely to play a role in causing severe hypertriglyceridemia than other forms of elevated TGs. *See, e.g.*, PX 925 at 000002, McKenney 2007 I at AMRN00290798 ("The higher the triglyceride level, the more likely genetics play a role. For example, triglyceride levels above 500 mg/dl are often seen in patients with familial hypertriglyceridemia[.]"). To this day, that remains the understanding. *See* PX 289 at 000041, FDA Medical Review, NDA No. 202057 (July 25, 2012) at ICOSAPENT_DFNDT00015464 ("[p]atients with very high TG have a strong genetic component to their disease[.]"); PX 269 at 000012, Miller et al., *Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association*, 123 Circulation 2292 (2011) at AMRN03146618 (Table 5 lists "Genetics" as the primary cause of

severe hypertriglyceridemia). In contrast to patients with borderline or high TG levels, it is unusual for very high TG levels to be attributed solely to diet and lifestyle.

115. It was also understood at the time of the invention that individuals with severely elevated TG levels responded differently to TG-lowering medications than individuals with borderline-high or high TGs. For example, the TG-lowering fibrate product TRICOR® increased LDL-C levels by a placebo-adjusted ***49.2%*** in patients with TG levels of at least 500 mg/dl, but only by a placebo-adjusted ***2.5***% in patients with baseline TGs between 350-499 mg/dl. PX 388 at 000007, TRICOR® Label (2004) at AMRN-PEXP-0001921, Table 2. In persons with even lower TG levels (mean of 231.9 mg/dl), TRICOR® actually *decreased* LDL-C by 14.5% compared to placebo. *Id*. at 000006, Table 1; *see also* PX 1027 at 000031, Mahley et al., *Drug Therapy for Hypercholesterolemia and Dyslipidemia, in The Pharmacological Basis of Therapeutics* (Goodman Gilman et al. eds., 11th ed. 2005) at AMRN-PEXP-0008364 ("The second-generation agents, such as fenofibrate, bezafibrate, and ciprofibrate, lower VLDL levels to a degree similar to that produced by gemfibrozil, but they also are more likely to decrease LDL levels by 15% to 20%. In patients with more marked hypertriglyceridemia (e.g., 400 to 1000 mg/dl), a similar fall in triglycerides occurs, but LDL increases of 10% to 30% are seen frequently.") With TG-lowering fish oil treatments that pre-dated VASCEPA®, the prior art warned that "the higher [a patient's] triglyceride level, the greater the rise in LDL-C tends to be," and "[a]s with fibrates, the degree of LDL-C elevations observed with P-OM3 [omega-3 fatty acid] treatment is generally related to the pretreatment TG levels. P-OM3 increases LDL-C levels the most in patients with the highest pretreatment TG levels." PX 1029 at 000017, Harris, W., *Fish Oils and Plasma Lipid and Lipoprotein Metabolism in Humans: A Critical Review*, 30 J. Lipid Research 785 (1989) at ICOSAPENT_DFNDTS00010010; PX 414 at 000010–12, Bays 2008 I.

116. It was known that administration of the omega-3 fatty acid treatment LOVAZA® produced much larger increases in LDL-C in individuals with severely elevated TGs than in individuals with high TGs. *See* PX 1034 at 000003, LOVAZA® PDR at

ICOSAPENT_DFNDTS00006712, Table 2 (noting that LDL-C increased by a median of 44.5% compared to baseline in patients with severely elevated TGs, with a placebo-adjusted increase of 49.3%); PX 939 at 000006, U.S. Dep't of Health & Human Servs. Food & Drug Admin., Approval Package NDA 21-654 (2004) at 5 ("LOVAZA® Statistical Review") (noting that LOVAZA® increased LDL-C by a median of 4.5% from baseline in patients with high TGs, with a placebo-adjusted increase of 6.9%). At the time of the invention, omega-3 fatty acids were understood to lower triglycerides at least in part by enhancing clearance of VLDL to LDL. Because persons with very high triglycerides were understood to possess a large excess of VLDL, a person of ordinary skill would have understood that the consequence of lowering triglycerides with omega-3 fatty acids in persons with very high triglyceride levels was to increase LDL, and therefore LDL-C, levels.

117. The FDA itself recognized the distinction between patients with very high TGs and patients with borderline-high or high TGs in its regulatory review process, as reflected by the FDA's recognition of a discrete indication for patients having TG levels of at least 500 mg/dl. *See* PX 566 at 000001, LOVAZA® Label 2007 at AMRN01187779 ("INDICATIONS AND USAGE . . . Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) triglyceride levels."). The recognition of this distinction by the FDA was further in keeping with the understanding at the time of the invention that patients with severely elevated TG levels had different primary treatment needs and may have different causes for elevated triglyceride levels than individuals with borderline high or high triglyceride levels.

E. Treatment of Severe Hypertriglyceridemia

118. For individuals with very high triglyceride levels, ATP-III recommended a combination of lifestyle changes (*i.e.*, increased exercise and a diet lower in carbohydrates, fat, and alcohol) and medication to lower TG levels. PX 989 at 000192–194, ATP-III at AMRN00290106–08.

1. General Approach to Treating Severe Hypertriglyceridemia

119. As noted above, it is understood that severe hypertriglyceridemia is driven by genetics. *See supra* ¶ 114. For example, the FDA has recognized that "patients with very high TG have a strong genetic component to their disease." PX 289 at 000041, FDA Medical Review, NDA No. 202057 (July 25, 2012) at ICOSAPENT_DFNDT00015464. Accordingly, severe hypertriglyceridemia is recognized as a chronic condition, which requires long-term treatment.

120. Lifestyle changes are generally insufficient to address severe hypertriglyceridemia. Pharmaceutical intervention is required. *See id.* at 000011. The FDA Medical Review also acknowledges, "[i]n addition to very low fat diets and increased physical activity, TG lowering drugs are usually required in persons with very high TG to prevent acute pancreatitis." *Id.*

121. This understanding that severe hypertriglyceridemia requires long-term pharmacotherapy is supported by literature with which clinicians are generally familiar. *See* PX 288 at 000010, Karalis, *A Review of Clinical Practice Guidelines for the Management of Hypertriglyceridemia*, 34 Adv Ther 300 (2017) ("Karalis") at AMRN-PEXP-0001524 (advising, "once the TGs are lowered consideration should be given to *adding a statin to their TG-lowering therapy*") (emphasis added).

122. Long-term treatment of severe hypertriglyceridemia is consistent with other uses of lipid management pharmaceuticals. *See, e.g.*, PX 277 at 000026, Jacobson et al., *National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia*, 9 J. Clinical Lipidology 129 (2015) at AMRN-PEXP-0009335 (when administering statin therapy, "[o]nce goal levels of atherogenic cholesterol have been achieved, response to therapy should be monitored periodically, and within 4 to 12 months, to confirm continued success in maintenance of goal levels and adherence."). Clinicians understand this to mean that therapy is continued and monitored to maintain the reduced lipid levels, even after reaching goal levels.

123. Moreover, without continued medication, patients' TG levels can rise back to their fasting baseline levels. PX 288 at 000010, Karalis 2017 at AMRN-PEXP-0001524. Thus, once severely hypertriglyceridemic patients' TGs are reduced below 500 mg/dL, the secondary goal of addressing cardiovascular risk is addressed by the addition of a statin, but the primary goal of avoiding the risk of pancreatitis is achieved by maintaining patients on their TG lowering medication. *Id.*

124. At the time of the invention, FDA-approved drugs for lowering TGs in patients with severe hypertriglyceridemia included (1) niacin, (2) fibrates, and (3) the omega-3 fatty acid medication LOVAZA®, also known as OMACOR®. But all of these products had limitations, including that they posed concerns about serious side effects, increased levels of LDL-C, or both.

125. Indeed, by March 2008, the prior art had long-reflected that a "substantial rise in LDL cholesterol" resulting from hypertriglyceridemia treatments was of "*major clinical concern*." PX 1026 at 000007, Carlson et al., *On the Rise in Low Density and High Density Lipoproteins in Response to the Treatment of Hypertriglyceridaemia in Type IV and Type V Hyperlipoproteinaemias*, 26 Atherosclerosis 603 (1977) ("Carlson") at AMRN-PEXP-0008186 (1977) ("The finding of *major clinical concern* in this report is the sometimes quite substantial rise in LDL cholesterol. This may be quite atherogenic and theoretically the benefit of lowering VLDL in these patients may be overridden by the potential danger due to the rise in LDL. This effect clearly stresses the necessity to consider the effect of treatment of HLP on the various lipoprotein classes.").

2. Niacin

126. Niacin, or nicotinic acid, had been used for decades to treat dyslipidemia. PX 883 at 000007, Levy, *Drugs Used in the Treatment of Hyperlipoproteinemias, in The Pharmacological Basis of Therapeutics* 834 (Goodman & Gilman eds., 6th ed. 1980) ("Goodman & Gilman") at AMRN-PEXP-0001601. Two niacin products approved for use in the United States at the time of the invention were NIACOR® and NIASPAN®. *See* PX 887 at 000002, NIASPAN® Physicians' Desk Reference (53d ed. 1999) ("NIASPAN® PDR") at

AMRN-PEXP-0001714; PX 885, NIACOR® Label (2000) ("NIACOR® Label 2000"); PX 886, NIACOR® Physicians' Desk Reference 3239 (57th ed. 2003) ("NIACOR® PDR").

127. Prior art reported that patients with very high TGs treated with niacin experienced "pronounced" increases in LDL-C and that these LDL-C increases were of "*major clinical concern*." PX 1026 at 000003, 000007, Carlson at AMRN-PEXP-0008182, AMRN-PEXP-0008186.

128. In addition to the major clinical concern with pronounced increases in LDL-C, serious side effects had long limited the use of niacin. *See, e.g.*, PX 883 at 000007, Levy at AMRN-PEXP-0001601 ("There are several untoward effects of nicotinic acid that limit its usefulness. Notably, the drug products intense cutaneous flush and pruritus. While these reactions decrease in intensity in most individuals after they have been on therapy for several weeks, they are unpleasant and result in poor compliance."); PX 989 at 000173–74, ATP-III at AMRN00290087–88 ("Nicotinic acid therapy can be accompanied by a number of side effects. . . . Since many nicotinic acid preparations are available without a prescription, persons should be instructed that nicotinic acid is associated with many severe adverse effects and regular monitoring by a health professional is essential."); *see also* PX 921 at 000024, Mahley at AMRN00290381 ("Two of niacin's side effects, flushing and dyspepsia, limit patient compliance."); PX 925 at 000004, McKenney 2007 I at AMRN00290800 ("Adverse effects associated with niacin . . . can limit their use.").

129. Among these side effects was flushing, which made niacin products difficult and unappealing to use for many patients. *See, e.g.*, PX 883 at 000007, Goodman & Gilman at AMRN-PEXP-0001601; PX 921 at 000024, Mahley at AMRN00290381; PX 925 at 000004, McKenney 2007 I at AMRN00290800; PX 864 at 000002, Carey, *FDA Rejects Merck's Cordaptive*, Bloomberg Law (Apr. 29, 2008), https://www.bloomberg.com/news/articles/2008-04-29/fda-rejects-merckscordaptivebusinessweek-business-news-stock-market-and-financial-advice ("Carey") at AMRN-PEXP-0001203 ("But high doses of niacin have side effects; lots of

them. . . . The most problematic one, which leads many people to stop taking the drug, is flushing of the skin.").

130. Flushing gave patients the very uncomfortable sensation of prickly heat along their abdomen and other parts of the body, and caused reddening of the skin, including the face. Clinical trials have reported that flushing impacts close to 90% of subjects using niacin-based products. *See, e.g.*, PX 887 at 000005, NIASPAN® PDR at AMRN-PEXP-0001717 ("In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching, and/or tingling) were the most common treatment-emergent adverse events (reported by as many as 88% of patients) for NIASPAN").

131. In addition to flushing, niacin was also associated with the risk of rhabdomyolysis (a condition involving muscle breakdown that can lead to kidney failure), gout, and peptic ulcer disease. *Id*. at 000004–05; PX 885 at 000004–05, NIACOR® Label 2000 at AMRN-PEXP-0001670–71. It had been known since at least 1995 that rhabdomyolysis with niacin was a particular concern when administered with a statin. *See* PX 876 at 000005, Garnett, *Interactions with Hydroxymethylglutaryl-coenzyme A Reductase Inhibitors*, 52 Am. J. Health-System Pharmacy 1639, AMRN-PEXP-0001434 (1995).

132. Many individuals with TGs of at least 500 mg/dl are diabetic, and niacin presented additional concerns for diabetics. Niacin is associated with severe side effects in diabetic patients. Niacin "reduces insulin sensitivity, and higher doses (>3 g/day) often worsen hyperglycemia in persons with type 2 diabetes." PX 989 at 000173, 000175, ATP-III at AMRN00290087, AMRN00290089. The 2008 ADA Standards of Care provided that when treating diabetic patients' severe hypertriglyceridemia with niacin, only "modest doses of 750–2000 mg/day" should be used to avoid this dangerous rise in glucose. PX 393 at 000016, ADA Standards of Medical Care (2008) at AMRN00098025. However, the niacin dose referenced in the 2008 ADA Standards of Care are insufficient to adequately lower severely elevated triglycerides. Currently, the 2019 ADA Standards of Care acknowledges that combination treatment with a statin and niacin has been associated with "an increased incidence of new-onset

diabetes . . . and disturbances in diabetes control among those with diabetes." PX 410 at 000120, American Diabetes Association, *Standards of Medical Care in Diabetes-2019*, 42 Diabetes Care S1, AMRN-PEXP-0007867 (2019). Based on the evaluation of risks versus benefits, the ADA expressly states that "combination therapy with a statin and niacin is not recommended." *Id.*

3. Fibrates

133. At the time of the invention, fibrate products, including LOPID®, TRICOR®, and TRILIPIX®, had also been approved to treat patients with very high TG levels. But these products also had considerable limitations, including that they caused large increases in LDL-C and posed risks of rhabdomyolysis if combined with a statin (especially with the fibrate gemfibrozil). *See* PX 964 at 000002–03, LOPID®, Physicians' Desk Reference (44th ed. 1990) ("LOPID® PDR 1990") at AMRN-PEXP-0001612–13; PX 828 at 000003, TRICOR®, Physicians' Desk Reference (62d ed. 2008) ("TRICOR® PDR II") at AMRN00291161; PX 937 at 000001, 000027, 000030, TRILIPIX® Label (2008) ("TRILIPIX® Label 2008") at AMRN01598389, AMRN01598415, AMRN01598418.

134. ***LOPID®***. LOPID® (gemfibrozil) was approved in 1981. Starting in 1990, the LOPID® product label warned of an LDL-C increase in patients with very high TGs, reflecting a longstanding concern about LDL-C increases. *See* PX 964 at 000002, LOPID® PDR 1990 at AMRN-PEXP-0001612 ("In some patients with high triglycerides levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol."). The prescribing information for LOPID® therefore explained that "[p]atients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil." *Id.*

135. The rise of LDL-C with LOPID® could not be addressed through concomitant use of a statin. Because gemfibrozil blocks the metabolic pathways for statin disposal, leading to statin accumulation in the blood and an unacceptable risk of rhabdomyolysis, LOPID® could not safely be combined with a statin. *See, e.g.*, PX 878 at 000002, Gorriz et al., *Rhabdomyolysis and Acute Renal Failure Associated With Gemfibrozil Therapy*, 74 Nephron 437 (1996) at AMRN-PEXP-0001460. The LOPID® prescribing information therefore "absolutely contraindicated" the

combination of LOPID® and cerivastatin, and observed generally that the combination of LOPID® with statins was "associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure and death." PX 825 at 000003, LOPID®, Physicians' Desk Reference (58th ed. 2004) ("LOPID® PDR 2004") at AMRN00290576.

136. The dangers associated with combining LOPID® with statins was a major limitation of gemfibrozil. The potential drug-drug interaction made it unsafe to use a statin to try to counteract the rise in LDL-C that LOPID® caused in persons with severe hypertriglyceridemia. In addition, the combination could not be used to address cardiovascular risk.

137. ***TRICOR®***. TRICOR® (fenofibrate) was another fibrate approved for use in patients with very high TGs. PX 828, TRICOR® PDR II. TRICOR® was approved in 2001. But as with LOPID®, an increase in LDL-C in the very high TG group was a concern with TRICOR®. The TRICOR® product label reported that in the group having TG levels ranging from 500 to 1500 mg/dl (mean 726 mg/dl), LDL-C increased by 45% from baseline in individuals using TRICOR®, with a placebo-adjusted increase of 49.2%. PX 966 at 000004, TRICOR® PDR I at AMRN-PEXP-0001936, Table 2. As noted above, in hypertriglyceridemic patients with lower levels of elevated triglycerides, fenofibrate reduced triglycerides either with small 2.5% increase in LDL-C (for those with TGs between 300-499 mg/dl) or a 14.5% *decrease* in LDL-C (for those with a mean TG of 231.9 mg/dl). PX 388 at 000006, 000007, TRICOR® Label at AMRN-PEXP-0001920 tbl. 1, AMRN-PEXP-000191 tbl. 2. Such increase in LDL-C in severely hyperlipidemic patients presented serious concerns about increased cardiovascular risk, and was not consistent with the ATP-III second priority of lowering LDL-C and cardiovascular risk.

138. The median fasting baseline LDL-C levels in the TRICOR® and placebo severely hyperlipidemic patients was around 100 mg/dL. Generally, statins are indicated for patients with

LDL-C exceeding 100 mg/dL. So, before taking TRICOR®, these patients were on the borderline of requiring statin therapy. However, after taking TRICOR®, which increased their LDL-C by 45% from baseline, statin therapy became necessary.

139. Additionally, while severely hypertriglyceridemic patients taking TRICOR experienced a mean reduction in TG levels of 54.5% over the course of the study, patients who were on a placebo (and adjusting diet and lifestyle) experienced an increase in TG levels of 7.2%. PX 966 at 000004, TRICOR® PDR I at AMRN-PEXP-0001936, Table 2. This indicates that relying on diet and lifestyle adjustments without the medication results in increased TG levels for severely hypertriglyceridemic patients.

140. TRICOR® was also associated with concerns about rhabdomyolysis when used with a statin, though to a lesser extent than LOPID® (gemfibrozil). The product label explained that "the combined use of fibric acid derivatives and HMG-CoA reductase inhibitors [statins] has been associated . . . in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure" and that the "use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis." *Id*.

141. Even when doctors were willing to prescribe such course of treatment, the large increase in LDL-C in patients with very high TG levels was understood to blunt the effects of the statin, thereby interfering with ATP-III's second priority of cardiovascular risk reduction.

142. ***TRILIPIX***®. Initially approved in 2008, TRILIPIX®, like TRICOR®, is a fenofibrate. TRILIPIX® was developed as part of a broader attempt to find a TG-lowering agent that could reduce cardiovascular risk over and above the cardiovascular risk provided by statin therapy. As part of that objective, TRILIPIX® was developed in an attempt to find a fibrate that, unlike LOPID®, could safely be used in combination with a statin.

143. But as with TRICOR®, TRILIPIX®'s prescribing information warned of a 45% increase in LDL-C from baseline in subjects with severely elevated TGs, and noted that "[t]reatment of patients with elevated TG often results in an increase of LDL-C (Table 7)." PX

937 at 000027, TRILIPIX® Label 2008 at AMRN01598415, Table 7 (reporting 45% increase in LDL-C from baseline with a placebo-adjusted increase in LDL-C of 49.2%). As noted above, such an increase in LDL-C presented concerns about increased cardiovascular risk, and was not consistent with the ATP-III second priority of lowering LDL-C and cardiovascular risk. More generally, TRILIPIX® ultimately failed to show a significant benefit in cardiovascular risk reduction over and above the risk reduction provided by statin therapy.

144. Additionally, as with the other fibrates, TRILIPIX® was associated with concerns about rhabdomyolysis, especially when used in conjunction with a statin, as well as other side effects such as muscle pain and weakness. PX 937 at 000030, 000032, TRILIPIX® Label 2008 at AMRN01598418, AMRN01598420. Thus, TRILIPIX® suffered from the same shortcomings as TRICOR®.

4. LOVAZA®

145. TG-lowering medications also included omega-3 fatty acid treatments. Omega-3 fatty acids include eicosapentaenoic acid ("EPA") and docosahexaenoic acid ("DHA"), which are found at relatively high levels in certain fatty fish and other seafood.

146. At the time of the invention, FDA had approved only one prescription omega-3 fish oil for very high TG patients, which was a product known as LOVAZA®. LOVAZA® was made from a mix of omega-3 fatty acid ethyl esters, of which the principal components are approximately 465 mg EPA and 375 mg DHA in ethyl ester form. *See* PX 922 at 000002, LOVAZA® PDR at AMRN00290592. This drug had also previously been known and marketed in the United States as OMACOR®.[2]

147. An advantage of LOVAZA® and omega-3 products generally was that they avoided the drug-drug interaction concerns of fibrates (*i.e.*, safety concerns about combination with a statin), and the side effect problems of niacin (including flushing).

[2] The ethyl ester form of EPA is known interchangeably as icosapent ethyl, ethyl-EPA, eicosapentaenoic acid ethyl ester, ethyl ecisoapentaenoate, and ethyl ecisoapent. The ethyl ester form of DHA is known most commonly as docosahexaenoic acid ethyl ester.

148. But while LOVAZA® generally had a better safety and side effect profile than fibrates or niacin-based products, it too was associated with a large increase in LDL-C in patients with severely elevated TG levels. As reported in the product's prescribing information, LOVAZA® increased LDL-C in persons with very high TGs by 49.3% compared to placebo. *Id.* at 000003, Table 2. As with fibrates, these increases raised (and still raise) concerns given the link between LDL-C and atherosclerosis. Because LOVAZA® increased LDL-C to such a degree in the very high TG population, the LOVAZA® labeling warned physicians that patients "should be monitored to ensure that the LDL-C level does not increase excessively." *Id.*

149. Additionally, because LOVAZA® dramatically increased LDL-C levels in individuals with very high TG levels, it ran counter to the goal of ATP-III of lowering LDL-C levels, and meant that it could not be administered as a monotherapy, but would instead also require concomitant statin use in an attempt to offset the LDL-C increase. LOVAZA® also interfered with statin use in people with very high TGs trying to use statins to lower LDL-C levels, as the substantial increases in LDL-C with LOVAZA® blunt the LDL-C lowering effect of a statin.

150. LOVAZA®'s prescribing information reported that patients experienced a 44.9% reduction in TG levels, while patients taking placebo (and adjusting diet and lifestyle) experienced a 6.7% increase in their TG levels. *Id.* This demonstrates, as with fibrates, that diet and lifestyle changes alone, do not reduce TG levels for patients with severe hypertriglyceridemia.

F. Prior absence of TG-lowering medications that reduce residual cardiovascular risk

151. In addition to the fact that there was no safe and well-tolerated TG-lowering agent that avoided both serious side effects and substantial LDL-C increases in individuals with very high TGs, there was also no safe TG-lowering agent that significantly lowered cardiovascular risk over and above the risk reduction provided by appropriate statin therapy, *i.e.*, statin therapy that helped patients achieve well-controlled LDL-C levels, historically ≤ 100 mg/dl.

152. Epidemiological studies had shown that elevated TG levels were associated with cardiovascular risk. There was accordingly a possibility that lowering TGs might provide a cardiovascular benefit, and in a manner that differed from the mechanism by which statins were understood to reduce cardiovascular risk (*i.e.*, reduction of LDL-C). That possibility gave rise to the desire to find a TG-lowering agent that could significantly lower cardiovascular risk beyond the risk reduction provided by statin therapy, which did not fully address cardiovascular risk. But a need for such agent remained as of March 2008, as no such TG-lowering agent had been found.

153. The strong interest in finding a triglyceride-lowering drug that would reduce cardiovascular risk stretched back decades prior to the invention. For example, efforts to find a fibrate that would lower cardiovascular risk began in the 1970s and continued into the 1990s and 2000s. *See infra* ¶¶ 907–14. Similar efforts were carried out with niacin-based formulations and various omega-3 fatty acids in the decades leading up to the invention. *See infra* ¶¶ 915–56. As noted above, the focus on a TG-lowering agent that would lower cardiovascular risk flowed at least in part from the fact that elevated TG levels have long been associated with increased risk of cardiovascular disease. *See, e.g.*, PX 846 at 000001, Austin et al., *Hypertriglyceridemia as a Cardiovascular Risk Factor,* 81 Am. J. Cardiology, Vol. 81 7B (1998) at AMRN01400315.

154. As the 1990s progressed, large statin trials provided clear evidence that statins were effective in the prevention of cardiovascular disease.[3] As statins became a standard treatment for reducing cardiovascular risk, the interest in finding a TG-lowering drug that could

[3] PX 845, Scandinavian Simvastatin Survival Study Group, *Randomised Trial of Cholesterol Lowering in 4444 Patients With Coronary Heart Disease: the Scandinavian Simvastatin Survival Study (42)*, 344 Lancet (1994); PX 840, Shepherd et al., *Prevention of Coronary Heart Disease With Pravastatin in Men With Hypercholesterolemia*, 333 N. Eng. J. Med. (1995); PX 839, Sacks et al., *The Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients With Average Cholesterol Levels*, 335 N. Eng. J. Med. (1996); PX 838, The Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study Grp., *Prevention of Cardiovascular Events and Death With Pravastatin in Patients With Coronary Heart Disease and a Broad of Initial Cholesterol Levels*, 339 N. Eng. J. Med. (1998).

lower cardiovascular risk shifted primarily to finding a TG-lowering drug that could lower *residual* cardiovascular risk—*i.e.*, cardiovascular risk that exists even after LDL-C levels are relatively well-controlled with statin therapy.

155. A reflection on the longstanding interest in identifying a TG-lowering agent that could lower cardiovascular risk is the numerous clinical trials that were carried out to assess whether various TG-lowering agents could lower cardiovascular risk, especially on top of statin therapy. These included trials on fibrates, niacin, and omega-3 fatty acids. *See infra* ¶¶ 907–25, 944–56. None of these previous trials showed significant cardiovascular risk reduction over and above the risk reduction provided by appropriate statin therapy.

VIII. DEVELOPMENT OF VASCEPA®

A. VASCEPA®

156. VASCEPA® is a highly purified preparation of ethyl EPA, also known as icosapent ethyl. FDA first approved VASCEPA® in July 2012 as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." PX 266 at 000001–06, 000017, NDA Approval Letter (July 26, 2012) at AMRN02973175–80, AMRN02973191; *see also* PX 940 at 000001–02, VASCEPA® Prescribing Information (2017) at AMRN03132168–69.

157. Amarin currently markets VASCEPA® in both 1 g and 500 mg capsules. *See* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169; Joint Stipulated Facts ¶¶ 181–82, 201 (ECF No. 324).

158. The daily dose of VASCEPA® is 4 grams per day, taken as two 1-gram (or four 500 mg) capsules twice daily with food. *See* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169; Joint Stipulated Facts ¶ 202 (ECF No. 324).

159. As a highly purified EPA product, VASCEPA® differs from LOVAZA® the only prior FDA-approved omega-3 fatty acid pharmaceutical product. Whereas LOVAZA® mixed two types of omega-3 fatty acid esters—EPA and DHA, *see* ¶ 145, *supra*—the pharmaceutical composition in VASCEPA® is more than 96% ethyl EPA, with little to no DHA, *see, e.g.*, PX

940 at 000004, VASCEPA® Prescribing Information (2017) at AMRN03132171; Joint Stipulated Facts ¶¶ 205–209 (ECF No. 324).

160. VASCEPA® has successfully addressed the limitations of LOVAZA® and the other prior art medications used for lowering TGs in patients with very high TGs: it lowers TGs without substantially increasing LDL-C (indeed, while reducing the level of atherogenic apoB particles in the blood, a cardiovascular risk factor) and without raising concerns about serious side effects; it can be combined with a statin without safety concerns or interfering with the statin's effect; it can safely and effectively be administered as either a monotherapy or in combination with other medications in individuals with severe hypertriglyceridemia; and, as recently demonstrated, VASCEPA® dramatically and unexpectedly reduces cardiovascular risk over and above the cardiovascular risk reduction provided by appropriate statin therapy.

161. During development, Amarin demonstrated VASCEPA®'s unique properties through clinical trials, including three studies known as MARINE, ANCHOR, and REDUCE-IT.

B. Clinical Trials

1. MARINE Trial

162. The MARINE trial was a phase 3, multi-center, placebo-controlled, randomized, double-blind twelve-week study with an open-label extension to evaluate the efficacy and safety of AMR 101—the name for the investigational product that ultimately has been marketed as VASCEPA®—in patients with TG levels ≥ 500 mg/dl and ≤ 2000 mg/dl. *See* PX 807, Amarin Pharma Inc., Clinical Study Report, *Study AMR-01-01-0016, A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥500 mg/dL & ≤2000 mg/DL: The AMR101 MARINE Study* (2011) ("MARINE Clinical Study Report"); *see also* PX 504, Bays et al., *Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label Extension [MARINE] Trial),* 108 Am. J. Cardiol. 682 (2011) ("Bays 2011").

163. The primary objective of the MARINE trial was to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering TGs in patients with fasting TG levels between 500 and 2,000 mg/dl. PX 807 at 000003, MARINE Clinical Study Report at AMRN00053459. The study also had a number of secondary objectives, including assessing the effect of AMR101 on other major lipoprotein lipid parameters, including total cholesterol, LDL-C, and apoB. *See id.* at 000003–04; *see also* PX 504, Bays 2011.

164. Patient enrollment in MARINE began in December 2009 and the last patient visit was completed in October 2010. PX 504 at 000002, Bays 2011 at AMRN03144928. In total, 229 patients were enrolled and randomized. *Id.* at 000003. Amarin reported the top-line results from MARINE in November 2010. PX 822, Amarin, Pharma Inc., *Amarin's AMR101 Meets Pivotal Phase 3 Study Endpoints With Highly Statistically Significant Reductions in Triglycerides at 4 Gram and 2 Gram Doses in MARINE Trial With No Statistically Significant Increase in LDL-C and Safety Profile Similar to Placebo* (Nov. 29, 2010), https://investor.amarincorp.com/news-releases/news-release-details/amarins-amr101-meets-pivotal-phase-3-study-endpoints-highly.

165. The MARINE trial demonstrated that use of VASCEPA® in patients with severely elevated TG levels lowered TGs without increasing LDL-C. In a daily dose of 4 g, VASCEPA® reduced TGs by a placebo-adjusted median of 33.1%, and apoB by a placebo-adjusted median of 8.5%, while not increasing LDL-C, over the course of twelve weeks. PX 504 at 000003–05, Bays 2011 at AMRN03144929–31; PX 807 at 000071, 000079, 000082, MARINE Clinical Study Report at AMRN00053527, AMRN00053535, AMRN00053538.

166. The MARINE trial also revealed that use of VASCEPA® in patients with severely elevated TGs who were on a statin resulted in a TG reduction from baseline of 29.5%, with a placebo-adjusted reduction in TGs of 61.8%. PX 807 at 000434, MARINE Clinical Study Report at AMRN00053890. Such individuals experienced an 8.5% reduction in LDL-C from baseline, with a placebo-adjusted reduction in LDL-C of 1.8%. *Id.* at 000459. Individuals with TGs ≥ 500 mg/dl who were not on a statin experienced a TG reduction from baseline of 26.4%,

with a placebo-adjusted reduction in TGs of 32.8%. These individuals also experienced a 1.5% reduction in LDL-C, with a placebo-adjusted reduction in LDL-C of 1.3%. *Id.* at 000434, 000460.

167. The MARINE trial further showed that VASCEPA® is safe and extremely well tolerated, with a safety profile similar to that of the placebo. *See* PX 504 at 000007, Bays 2011 at AMRN03144933, Table 4. The 4 g preparation did not exceed placebo in collective treatment emergent adverse events, or in the individual adverse events of diarrhea, nausea, or eructation. *Id.* The most common treatment emergent adverse events were gastrointestinal (*i.e.* diarrhea, nausea, and eructation), with the greatest numerical incidence in the placebo group. *Id.* No more than 1% of subjects in the AMR 101 4g/day group experienced any of these events, and no one in the AMR 101 4g/day experienced eructation. *Id.* No deaths occurred, and only 1 serious event was reported in the AMR 101 4g/day group (coronary artery disease), but this was not deemed to be related to the study drug. *Id.* AMR 101 4g/day produced no significant changes in vital signs, electrocardiographic parameters, alanine aminotransferase, aspartate aminotransferase, or creatine kinase values. *Id.*

2. ANCHOR Trial

168. ANCHOR was a phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial to assess the efficacy and safety of AMR101 (VASCEPA®) in statin-treated patients at high cardiovascular risk with well-controlled LDL cholesterol and residually high TG levels (≥200 and <500 mg/dl). *See* PX 942 at 000002, Ballantyne et al., *Efficacy and Safety of Eicosapenaetaenoic Acid Ethyl Ester (AMR 101) Therapy in Statin-Treated Patients with Persistent high Triglycerides (from the ANCHOR Study),* The Am. J. of Cardiology (2012) ("Ballantyne") at AMRN03144839; *see also* PX 808, Amarin Pharma Inc., *Clinical Study Report, A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (≥ 200 mg/dL and ≤ 500*

mg/dL) Despite Statin Therapy: The AMR101 ANCHOR Study, 2011 ("ANCHOR Clinical Study Report").

169. In 2009, Amarin entered into an agreement with FDA relating to a proposed additional indication for VASCEPA®—called the Special Protocol Assessment ("SPA") Agreement for the ANCHOR study. PX 1146, FDA, Special Protocol - Agreement. The agreement provided that Amarin would conduct the requested 12-week lipid endpoint trial—which was ultimately called the ANCHOR trial—to determine whether VASCEPA® lowers triglyceride levels in statin-treated patients with well-controlled LDL-C levels and high triglyceride levels (200–499 mg/dl). In essence, the agreement and related regulatory dialogue provided that if the ANCHOR trial met its study endpoints, and if Amarin enrolled 50% of subjects in the requested cardiovascular outcome trial—which ultimately became the REDUCE-IT study—FDA would grant Amarin an indication to market VASCEPA® to treat patients with high triglyceride levels (200–499 mg/dl) on background statin therapy.

170. The ANCHOR study was conducted at 97 sites in the United States from December 2009 through February 2011 with 702 patients. PX 942 at 000002–03, Ballantyne at AMRN03144839–40. The primary endpoint in the trial was the percentage change in triglyceride level from baseline compared to placebo after 12 weeks of treatment. *Id.* at 000002. Other secondary endpoints included the effect from baseline compared to placebo on other lipid parameters, including LDL-C, non-HDL-C, and apoB. *Id.*

171. When Amarin conducted the ANCHOR trial in 2011, the trial achieved its primary and secondary endpoints, demonstrating a statistically significant reduction in triglyceride levels in the VASCEPA® 4 g / day group compared with the placebo (mineral oil) groups (-21.5%) without increasing LDL-C relatively to placebo, and also demonstrated favorable outcomes with respect to other lipid parameters, including LDL-C (-6.2%), Lp-PLA2 (-19%), non-HDL-C (-13.6%), VLDL-C (-24.4%), and apoB (-9.3%). *See id.* 000005–06.

172. After obtaining these results, and following Amarin's enrollment of 50% of patients in the REDUCE-IT trial, Amarin in 2013 submitted a supplemental NDA ("sNDA") for

its additional proposed indication—seeking approval to market and sell VASCEPA® as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, apoB, LDL-C, TC (total cholesterol), and VLDL-C (very low-density lipoprotein cholesterol) in adult patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent.

173. But in October 2013, FDA rescinded the ANCHOR SPA, concluding that currently available evidence failed to support the hypothesis that a TG-lowering drug significantly reduces the risk for cardiovascular events among statin-treated patients, and that FDA did not believe that a change in triglyceride levels was sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in subjects with serum triglyceride levels below 500 mg/dl. This was based in part on the fact that the cardiovascular outcome trials that had been underway in 2008 when Amarin initially proposed its supplemental indication for VASCEPA®—including ACCORD-Lipid and AIM-HIGH—reported negative outcomes. Rescission of the ANCHOR SPA agreement was first discussed at the October 16, 2013 FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. *See generally* PX 986, U.S. Food & Drug Admin., Ctr. for Drug Evaluation and Research, Endocrinologic and Metabolic Drugs Advisory Committee Meeting Transcript (Oct. 16, 2013) ("EMDAC Transcript").

3. REDUCE-IT Trial

174. REDUCE-IT was a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted to evaluate the effectiveness of VASCEPA® as an add-on to statin therapy in reducing the first major cardiovascular event in a high-risk patient population compared to statin therapy alone. The results of this trial were published in the *New England Journal of Medicine* on November 10, 2018. *See* PX 272, Bhatt et al., *Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia*, 380 N. Eng. J. Med. 11 (2019) ("Bhatt NEJM 2019"). These results also appear in a study report on REDUCE-IT. PX 1189, Amarin Pharma Inc., *Clinical Study Report: A Multi-Center, Prospective, Randomized, Double-Blind, Placebo- Controlled, Parallel-Group Study to Evaluate the Effect of AMR 101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular*

Disease or at High Risk for Cardiovascular Disease REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial) (Feb. 27, 2019) ("REDUCE-IT Clinical Study Report").

175. REDUCE-IT studied patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who at enrollment had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). PX 272 at 000001, Bhatt NEJM 2019 at AMRN-PEXP-0000689; PX 1189 at 000009, 000061–62, REDUCE-IT Clinical Study Report at AMRN03172262, AMRN03172314–15. The patients were randomly assigned to receive 4 g per day of AMR101 or placebo. PX 272 at 000001, Bhatt NEJM 2019 at AMRN-PEXP-0000689; PX 1189 at 000008, REDUCE-IT Clinical Study Report at AMRN03172261.

176. The primary endpoint in REDUCE-IT was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. PX 272 at 000001, Bhatt NEJM 2019 at AMRN-PEXP-0000689; PX 1189 at 000004–05, 000051–52, 000078–79, REDUCE-IT Clinical Study Report at AMRN03172257–58, AMRN03172304–05, AMRN03172331–32.

177. The REDUCE-IT trial was a significant, multi-year undertaking spread across clinical sites in 11 different countries. Amarin invested several years and more than $350 million to designing and conducting the REDUCE-IT trial. The first patient underwent randomization in December 2011 and enrollment and randomization did not conclude until 2016. PX 272 at 000002, Bhatt NEJM 2019 at AMRN-PEXP-0000690. All told, Amarin enrolled a total of 8,179 patients (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. *Id.* at 000001; PX 1189 at 000007, 000055, 000057, 000120, REDUCE-IT Clinical Study Report at AMRN03172260, AMRN03172308, AMRN03172310, AMRN03172373. The REDUCE-IT patients commenced their final study visits in spring 2018, and Amarin announced top-line results in the fall of 2018. PX 678, Amarin Corporation,

REDUCE-IT™ Cardiovascular Outcomes Study of Vascepa® (icosapent ethyl) Capsules Met Primary Endpoint.

178. REDUCE-IT showed that use of VASCEPA® results in a remarkable degree of cardiovascular risk reduction, over and above the risk reduction provided by statin therapy, in patients whose LDL-C levels were well-controlled—with an LDL-C upper limit of 100 mg/dl—which is a level that ATP-III characterized as "optimal." PX 272 at 000002, Bhatt NEJM 2019 at AMRN-PEXP-0000690; PX 989 at 000023, ATP-III at AMRN00289937. Compared to placebo, VASCEPA® significantly reduced the risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis by 25%, among the patients who received VASCEPA® in two gram doses twice daily in addition to a statin. PX 272 at 000001, 000005, 000009–10, Bhatt NEJM 2019 at AMRN-PEXP-0000689, AMRN-PEXP-0000693, AMRN-PEXP-0000697–98 and Fig. 4; PX 1189 at 000017, 000137, REDUCE-IT Clinical Study Report at AMRN03172270, AMRN0317390. The risk of the key secondary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis was also significantly lower with VASCEPA® taken twice daily, by 26%, compared to placebo. PX 272 at 000009–10, Bhatt NEJM 2019 at AMRN-PEXP-0000697–98 and Fig. 4; PX 1189 at 000017, 000134, 000137, REDUCE-IT Clinical Study Report at AMRN03172270, AMRN03172387, AMRN03172390. VASCEPA® also reduced the occurrence of heart attack by 31%, revascularization (coronary stenting or bypass surgery) by 35%, death from cardiovascular causes by 20%, hospitalization for unstable angina by 32%, and stroke by 28%. PX 272 at 000010, Bhatt NEJM 2019 at AMRN-PEXP-0000698 and Fig. 4; PX 1189 at 000018, 000138–41, REDUCE-IT Clinical Study Report at AMRN03172271, AMRN03172391–94.

179. Moreover, REDUCE-IT showed that VASCEPA® is beneficial in reducing cardiovascular events in diabetics. PX 272 at 000006, Bhatt NEJM 2019 at AMRN-PEXP-0000694; PX 1189 at 000182, 000205, REDUCE-IT Clinical Study Report at AMRN03172435, AMRN03172458. The primary endpoint (cardiovascular death, nonfatal myocardial infarction,

nonfatal stroke, coronary revascularization, or unstable angina) was reduced by 23% in those with diabetes and there was no statistical difference in benefit between the diabetic and non-diabetic patients. And the key secondary endpoint (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) was reduced by 30% in those with diabetes, and there was no statistical difference in benefit between the diabetic and non-diabetic patients. PX 272 at 000008, Bhatt NEJM 2019 at AMRN-PEXP-0000696. REDUCE-IT, therefore, demonstrates a significant benefit in cardiovascular event reduction in patients with elevated CV risk, including diabetic patients.

C. FDA Approval

180. Anyone wishing to market a new drug that has not previously been approved by the FDA (a "pioneering" drug) must file a New Drug Application ("NDA") demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b).

181. Based on the results of the MARINE study, in 2011 Amarin filed an NDA (No. 202057) seeking FDA approval to market 1 g icosapent ethyl capsules, under the tradename VASCEPA®, for use in treatment of patients with severe hypertriglyceridemia. PX 1147, FDA Letter re NDA Acknowledgment (Sept. 27, 2011); PX 1148, FDA Letter re Acceptance of NDA 202057 (Dec. 8, 2011); PX 1149, FDA Summary Review NDA No. 202057 (July 26, 2012).

182. On July 26, 2012, FDA approved VASCEPA® (icosapent ethyl) 1 g capsules. The approved indication was "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." PX 266 at 000001, NDA No. 202057, NDA Approval (July 26, 2012) at AMRN02973175; Joint Stipulated Facts ¶ 180 (ECF No. 324).

183. Amarin Pharmaceuticals Ireland Limited is the current holder of NDA No. 202057. Joint Stipulated Facts ¶ 178 (ECF No. 324).

184. Amarin Pharma, Inc. is Amarin Pharmaceuticals Ireland Limited's agent in the United States for purposes of communicating with FDA regarding NDA No. 202057. Joint Stipulated Facts ¶ 179 (ECF No. 324).

185. FDA approved a 500 mg strength of VASCEPA® in February 2017. Joint Stipulated Facts ¶ 181 (ECF No. 324).

186. After reviewing the results of the REDUCE-IT study, FDA in December 2019 expanded the approved use of VASCEPA® to include reduction in cardiovascular risk in patients with TG levels over 150 mg/dl, including persons with very high TGs. In addition to the severe-hypertriglyceridemia indication first approved in July 2012, VASCEPA® is now also indicated

> as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.

See PX 1186 at 000001, VASCEPA® Prescribing Information (2019) at AMRN03174954.

187. The inclusion of patients with very high TGs in VASCEPA®'s cardiovascular risk reduction indication demonstrates FDA's view that the REDUCE-IT results apply to individuals with TGs of at least 500 mg/dl. Moreover, in approving the expanded indication, FDA removed the Limitation of Use that stated, "The effect of VASCEPA® on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined," thus recognizing VASCEPA®'s cardiovascular benefit in patients with very high TGs. *Compare* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169, *with* PX 1186 at 000002, VASCEPA® Prescribing Information (2019) at AMRN03174954. VASCEPA® is now the first FDA approved drug to reduce cardiovascular risk among patients with elevated TG levels as an add-on to maximally tolerated statin therapy, and the only drug approved for treatment of severe hypertriglyceridemia that has also been shown to provide cardiovascular benefit to patients on top of a statin.

IX. DEFENDANTS' GENERIC DRUGS

A. Abbreviated New Drug Applications

188. A person wishing to market a generic copy of a drug previously approved by FDA—known as the "Reference Listed Drug" ("RLD")—may follow a truncated approval process by filing an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j).

189. Unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. Instead, the ANDA applicant is permitted to rely on the prior approval of the RLD—in essence, piggybacking on the NDA application and safety and effectiveness conclusions. 21 U.S.C. § 355(j). An ANDA applicant may not establish new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved for the RLD. 21 U.S.C. § 355(j)(2)(A)(i).

190. An ANDA applicant must show that its proposed product is the "same as" the RLD, meaning it is "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use," though the applicant may omit "conditions of use" for which FDA cannot grant approval "because of exclusivity or an existing patent." 21 C.F.R. § 314.92(a)(1).

191. To obtain FDA approval under 21 C.F.R. § 314.105(d), an ANDA applicant in Defendants' position must show, among other things, that:

- The methods, facilities, controls used for manufacture, processing, and packing of the proposed drug product are adequate to "preserve its identity, strength, quality, and purity," 21 C.F.R. § 314.127(a)(1);
- FDA has already approved each proposed condition of use for the RLD, *id.* § 314.127(a)(2);
- The active ingredient(s) in the proposed ANDA product is (are) the same as the RLD, *id.* § 314.127(a)(3);
- The route of administration, dosage form, and strength for the proposed drug product are the same as for the RLD, *id.* § 314.127(a)(4);

- The proposed drug product is bioequivalent to the RLD, *id.* § 314.127(a)(6); and
- The labeling proposed for the drug is "the same as the labeling approved for the [RLD]," except for changes required because the proposed drug product and the RLD "are produced or distributed by different manufacturers or because the [RLD's] labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the [RLD] for all remaining, nonprotected conditions of use," *id.* § 314.127(a)(7).

B. Hikma's ANDA No. 209457

192. On July 26, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. submitted to FDA ANDA No. 209457 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA® (icosapent ethyl) 1 g capsules. Joint Stipulated Facts ¶ 183 (ECF No. 324).

193. VASCEPA® is the RLD for ANDA No. 209457. Joint Stipulated Facts ¶ 210 (ECF No. 324).

194. In a letter dated September 21, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that they had submitted ANDA No. 209457 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the Asserted Patents. Joint Stipulated Facts ¶ 185 (ECF No. 324); PX 1140 at 000002, Roxane Paragraph IV Letter (Sept. 21, 2016) at 2.

195. Thus, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. had knowledge of the Asserted Patents when they filed ANDA No. 209457. *See* PX 1156 at 000001, Roxane Paragraph IV Certification at WWIC0-NV-000079.

196. On October 31, 2016, Amarin filed a complaint for patent infringement against Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. in this Court, alleging that their submission of ANDA No. 209457 to obtain FDA's approval for a generic version of the 1 g strength of VASCEPA® before the expiration of the Asserted Patents constitutes infringement of

those patents under 35 U.S.C. § 271(e)(2), and that, if Hikma Pharmaceuticals and Roxane Laboratories, Inc. were to commercially use, offer for sale, or sell their generic version of VASCEPA®, or induce or contribute to such conduct, they would further infringe the Asserted Patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated the action as Case No. 2:16-cv-02525. *See* Case No. 2:16-cv-02525, ECF No. 1.

197. On or about December 8, 2016, Roxane Laboratories, Inc. transferred ANDA No. 209457 to West-Ward Pharmaceuticals International Limited. Joint Stipulated Facts ¶ 186 (ECF No. 324).

198. On or about December 8, 2016, West-Ward Pharmaceuticals International Limited appointed West-Ward Pharmaceuticals Corp. as its agent for purposes of communication with FDA regarding ANDA No. 209457. Joint Stipulated Facts ¶ 187 (ECF No. 324).

199. On February 24, 2017, the Court entered an order substituting West-Ward Pharmaceuticals International Limited and West-Ward Pharmaceuticals Corp. for Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. as Defendants in this action. *See* Case No. 2:15-cv-02525, ECF No. 52.

200. West-Ward Pharmaceuticals Corp. subsequently changed its name to Hikma Pharmaceuticals USA Inc. Joint Stipulated Facts ¶ 190 (ECF No. 324).

201. On August 2, 2018, the Court entered an order substituting Hikma Pharmaceuticals USA Inc. for West-Ward Pharmaceuticals Corp. as a Defendant in this action. *See* Case No. 2:16-cv-02525, ECF No. 132.

202. West-Ward Pharmaceuticals International Limited subsequently changed its name to Hikma Pharmaceuticals International Limited. Joint Stipulated Facts ¶ 189 (ECF No. 324).

203. On February 15, 2019, the Court entered an order substituting Hikma Pharmaceuticals International Limited for West-Ward Pharmaceuticals International Limited as a Defendant in this action. *See* Case No. 2:16-cv-02525, ECF No. 185.

204. On or about July 8, 2019, Hikma Pharmaceuticals International Limited transferred ANDA No. 209457 to Hikma Pharmaceuticals USA Inc. Hikma Pharmaceuticals USA Inc. is now the owner of ANDA No. 209457. Joint Stipulated Facts ¶ 191 (ECF No. 324).

C. DRL's ANDA No. 209499

205. On July 26, 2016, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA® (icosapent ethyl) 1 gram capsules. Joint Stipulated Facts ¶ 193 (ECF No. 324).

206. VASCEPA® is the RLD for ANDA No. 209499. Joint Stipulated Facts ¶ 222 (ECF No. 324).

207. In a letter dated September 22, 2016, DRL notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that it had submitted ANDA No. 209499 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the Asserted Patents. Joint Stipulated Facts ¶ 195 (ECF No. 324); PX 1142 at 000002, Dr. Reddy's Paragraph IV Letter (1 g) (Sept. 22, 2016) at 2.

208. Thus, DRL had knowledge of the Asserted Patents when it filed ANDA No. 209499. *See* PX 1157 at 000001, DRL Paragraph IV Certification at DRLEEPA 0000049.

209. On November 4, 2016, Amarin filed a complaint for patent infringement against DRL in this Court, alleging that DRL's submission of ANDA No. 209499 to obtain FDA's approval for a generic version of the 1 g strength of VASCEPA® before the expiration of the Asserted Patents constitutes infringement of those patents under 35 U.S.C. § 271(e)(2), and that, if DRL were to commercially use, offer for sale, or sell its generic version of VASCEPA®, or induce or contribute to such conduct, it would further infringe the Asserted Patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated the action as Case No. 2:16-cv-02562. *See* Case No. 2:16-cv-02562, ECF No. 1.

210. On January 10, 2017, the Court consolidated the DRL 1 g infringement action, Case No. 2:16-cv-02562, with the Hikma 1 g infringement action, Case No. 2:16-cv-02525, with

the latter case serving as the lead case. *See* Case No. 2:16-cv-02525, ECF No. 30; Case No. 2:16-cv-02562, ECF No. 28.

211. On or about July 11, 2018, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a supplement to ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA® (icosapent ethyl) 500 mg capsules. Joint Stipulated Facts ¶ 197 (ECF No. 324).

212. In a letter dated July 11, 2018, DRL notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that it had submitted the 500 mg supplement to ANDA No. 209499 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the '728, '715, '677, '652, and '929 patents. Joint Stipulated Facts ¶ 198 (ECF No. 324).

213. Thus, DRL had knowledge of the '728, '715, ' 677, '652, and '929 Patents when it filed the 500 mg supplement to ANDA No. 209499. *See* PX 1141, Dr. Reddy's Paragraph IV Letter (500 mg) (July 11, 2018).

214. On August 24, 2018, Amarin filed a complaint for patent infringement against DRL in this Court, alleging that DRL's submission of a supplement to ANDA No. 209499 seeking FDA approval to market a generic version of the 500 mg strength of VASCEPA® before the expiration of several patents, including the '728, '715, '677, '652, and '929 Patents, constitutes infringement of those patents under 35 U.S.C. § 271(e)(2), and that, if DRL were to commercially use, offer for sale, or sell its generic version of VASCEPA®, or induce or contribute to such conduct, it would further infringe these patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated that action as Case No. 2:18-cv-01596. *See* Case No. 2:18-cv-01596, ECF No. 1.

215. Amarin and DRL have stipulated that the final judgment in the consolidated 1 g infringement actions will bind Amarin and DRL as though that judgment were also made in the 500 mg infringement action. *See* Case No. 2:18-cv-01596, ECF No. 27.

D. Defendants' ANDA Products

216. In their respective ANDAs, Hikma and DRL seek FDA approval to market generic versions of VASCEPA® 1 g capsules as Icosapent Ethyl Capsules, 1 gram (individually, "Hikma's ANDA Product" and "DRL's ANDA Product") (collectively, "Defendants' ANDA Products"). Joint Stipulated Facts ¶¶ 213, 225 (ECF No. 324).

217. Defendants specifically seek approval to market their ANDA Products for use "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia"—the indication for which FDA first approved VASCEPA® in July 2012. Joint Stipulated Facts ¶¶ 212, 224 (ECF No. 324).

218. The active pharmaceutical ingredient in Defendants' ANDA Products is icosapent ethyl, which is the same active ingredient as in VASCEPA®. *See* Joint Stipulated Facts ¶¶ 215, 227 (ECF No. 324); PX 274 at 000004, 000009, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002838, WWIC0-NV-002843; PX 574 at 000009, 000016, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095599, DRLEEPA 0095606; PX 940 at 000004–05, 000010, VASCEPA® Prescribing Information (2017) at AMRN03132171–72, AMRN03132177.

219. Defendants have stipulated that the pharmaceutical composition in their ANDA Products—*i.e.* the drug substance inside their icosapent ethyl capsules—will be comprised of 96% or more ethyl EPA and less than 3–4% DHA or its esters, as required by the Asserted Claims. Joint Stipulated Facts ¶¶ 217–21, 229–34 (ECF No. 324).

220. If approved, Defendants' ANDA Products will be bioequivalent to VASCEPA®. Joint Stipulated Facts ¶¶ 211, 223 (ECF No. 324).

221. Like VASCEPA®, Defendants' ANDA Products, if approved, will be marketed as capsules that are intended to be administered orally and swallowed whole. PX 274 at 000002, 000004, 000007–08, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836, WWIC0-NV-002838, WWIC0-NV-002841–42; PX 574 at 000006, 000009, 000013, 000015, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596, DRLEEPA 0095599,

DRLEEPA 0095603, DRLEEPA 0095605; PX 940 at 000002, 000004–05, 000008–09, VASCEPA® Prescribing Information (2017) at AMRN03132169, AMRN03132171–72, AMRN03132175–76.

222. Like VASCEPA®, the daily dose of Defendants' ANDA Products, if approved, will be 4 grams per day, taken as two 1-gram capsules twice daily with food. Joint Stipulated Facts ¶¶ 214, 226 (ECF No. 324).

X. VASCEPA®'S AND DEFENDANTS' PROPOSED LABELING

223. As part of their ANDAs, Defendants submitted to the FDA proposed prescribing information for their ANDA Products. *See generally* PX 274, Hikma Proposed Prescribing Information (2016); PX 574, DRL Proposed Prescribing Information (2018).

224. Defendants proposed labeling largely copies the FDA-approved prescribing information for VASCEPA® that was in use prior to December 2019, when FDA approved new labeling incorporating VASCEPA®'s additional indication for cardiovascular risk reduction. *Compare* PX 940, VASCEPA® Prescribing Information (2017), *with* PX 274, Hikma Proposed Prescribing Information (2016), *and* PX 574, DRL Proposed Prescribing Information (2018).[4]

225. Prescription drug labels are referred to alternatively as the label, labeling, prescribing information, and/or package insert.

226. The primary purpose of a prescription drug label is to provide clinicians with a clear and concise statement of the information they need to use a drug safely and effectively. *See, e.g.*, PX 776 at 000004, FDA, *Guidance for Industry: Clinical Studies Section of Labeling*

[4] On December 30, 2019, Hikma updated its proposed labeling after FDA approved a new version of the VASCEPA® labeling. *See* PX 1203, Hikma Proposed Prescribing Information (2019); PX 1204, Hikma Side-By-Side Comparison to RLD Prescribing Information (Dec. 2019).

The sections of Hikma's labeling on which Amarin will rely to prove that Hikma intends to induce infringement of the Asserted Claims remain materially identical to the prior labeling. As a result, and given the late disclosure of Hikma's new proposed labeling, Amarin's proposed findings of fact and conclusions of law cite throughout to Hikma's prior proposed labeling. *See* PX 274, Hikma Proposed Prescribing Information (Dec. 2016).

for Human Prescription Drug and Biological Products — Content and Format (Jan. 2006) ("FDA Guidance for Industry: Clinical Studies Section") at AMRN-PEXP-0010190 ("The principal objective of labeling is to provide the information that is most useful to prescribers in treating their patients.").

227. To make it easier for clinicians to access, read, and use a drug label to make prescribing decisions, FDA has issued lengthy regulations and guidance documents setting out detailed guidelines for the content and format of prescription drug labels.

228. A prescription drug label is ordinarily divided into three sections: The Highlights of Prescribing Information, a Table of Contents, and the Full Prescribing Information. *See generally* 21 C.F.R.§ 201.57(a)–(c).

229. The Full Prescribing Information in a drug label is comprised of up to eighteen separate components: (1) Boxed Warning; (2) Indications and Usage; (3) Dosage and Administration; (4) Dosage Forms and Strengths; (5) Contraindications; (6) Warnings and Precautions; (7) Adverse Reactions; (8) Drug Interactions; (9) Use in Specific Populations; (10) Drug Abuse and Dependence; (11) Overdosage; (12) Description; (13) Clinical Pharmacology; (14) Nonclinical Toxicology; (15) Clinical Studies; (16) References; (17) How Supplied/Storage and Handling; and (18) Patient Counseling Information. *See* 21 C.F.R. § 201.57(c)(1)–(18).

230. The prescribing information for a drug is often accompanied by an information sheet or medication guide intended for the patient's use. *See* 21 C.F.R. § 201.57(c)(18).

231. To help clinicians navigate, understand, and utilize a prescription drug label when making prescribing decisions, FDA has instructed that "[d]etailed information about a particular topic should be consolidated in a single labeling section." PX 778 at 000008, FDA, *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (Feb. 2013) ("FDA Guidance for Industry: Labeling") at AMRN-PEXP-0010269. While "[o]ther sections of labeling may more briefly describe or refer to [a] topic," FDA advises that multiple sections should "not repeat the same content or level of detail." *Id.* Instead, applicants for new drugs should "identif[y], prioritize[],

and locate[]" the "[c]linical information pertinent to prescribing decisions . . . in the labeling section that most appropriately communicates [that] type of information." *Id.*

232. Because information critical to a clinician's understanding of how to use a drug safely and effectively is divided across several sections in any given drug label, FDA advises that the "labeling should be considered in its entirety for individual prescribing decisions." PX 573 at 000005, FDA, *Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (Draft)* (July 2018) ("FDA Guidance for Industry: Indications and Usage Section") at AMRN-PEXP-010246.

233. The subsections that follow describe the purpose and content of select sections of the VASCEPA® labeling and Defendants' substantively-identical proposed labeling.

A. Indications and Usage

234. The "primary role" of the Indications and Usage section of a drug label "is to enable health care practitioners to readily identify appropriate therapies for patients by clearly communicating the drug's approved indication(s)." PX 573 at 000005, FDA Guidance for Industry: Indications and Usage Section at AMRN-PEXP-010246.

235. To this end, the Indications and Usage section of a drug label describes the drug's FDA approved indication (*i.e.*, the use for which FDA has approved the drug). In doing so, this section must identify the disease, condition, or symptom for which the drug is approved and specify whether the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of that disease or condition. *Id.* at 000005, 000010–11.

236. This section also should include other information necessary to understand the scope of the approved indication, including whether the drug is approved only for use in selected patient groups or only as an adjunct to another form of concomitant therapy. *Id.* at 000010–12.

237. This section also must "limit duration of use" when "such a limited duration is essential to ensure the safe and effective use of the drug." *Id.* at 000016.

238. Where necessary, the Indications and Usage section also must separately identify any "limitations of use," which advise clinicians when there is "reasonable concern or

uncertainty among FDA's expert reviewers" as to whether it is advisable to use the drug under particular circumstances or in particular patient groups. *Id.* at 000013–16.

239. The Indications and Usage section of VASCEPA®'s labeling states that "VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.[5]

240. The Indications and Usage section thus instructs clinicians that VASCEPA® is approved (*i.e.*, safe and effective) for use in combination with diet to reduce TGs in adult patients with severe hypertriglyceridemia—without concomitant administration of any other medication.

241. The Indications and Usage section of VASCEPA®'s labeling does not specify a duration of use, meaning VASCEPA® is approved for long-term use. *Id.* The absence of a duration limitation advises clinicians that FDA has determined that there are no safety or efficacy concerns that require limiting the duration of use of VASCEPA®.

242. The Indications and Usage section of VASCEPA®'s labeling also includes a "Limitation of Use" advising clinicians that VASCEPA®'s effect on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. *Id.*[6]

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[5] The Indications and Usage section of VASCEPA®'s new labeling adds a second approved indication: "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." PX1186 at 000002, VASCEPA® Prescribing Information (2019) at AMRN03174955.

[6] Prior to December 2019, VASCEPA®'s labeling also included a "Limitation of Use" advising clinicians that VASCEPA®'s effect on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia had not been determined. *See* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. That "Limitation of Use" was dropped when FDA approved VASCEPA®'s new indication for cardiovascular risk-reduction. *See* PX 1186 at 000002, VASCEPA® Prescribing Information (2019) at AMRN03174955.

243. Defendants seek approval to market their ANDA Products for the same severe hypertriglyceridemia indication for which VASCEPA® is approved. The Indications and Usage section of Defendants' proposed labeling thus states that "[i]cosapent ethyl is indicated as an adjunct to diet to reduce triglycerides (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia." PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000005–06, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095595–96.

244. Like the VASCEPA® labeling, the Indications and Usage section of Defendants' proposed labeling does not specify a limited duration of use and does not recommend concomitant administration of any medication alongside Defendants' ANDA Products. *See* PX 274 at 000001–02, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835–36; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596.

245. Defendants' proposed labeling includes the same "Limitation of Use" regarding icosapent ethyl's effect on the risk of pancreatitis in patients with severe hypertriglyceridemia. *See* PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596.

B. Dosage and Administration

246. The Dosage and Administration section of a drug label instructs physicians on the approved dose, dosing regimen, and route of administration. *See* 21 C.F.R. § 201.57(c)(3).

247. Where necessary, the Dosage and Administration section also must identify "[t]he usual duration of treatment when treatment duration should be limited," *id.*, and any premedication or concomitant medications necessary to make the drug safe and effective, *see* PX 572 at 000007–08, FDA, *Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (Mar. 2010) ("FDA Guidance for Industry: Dosage and Administration Section") at AMRN-PEXP-0010235–36.

248. The Dosage and Administration section in VASCEPA®'s labeling states that the "daily dose" of VASCEPA® 1-gram capsules is "4 grams per day" taken as "two 1-gram capsules twice daily with food." PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

249. The Dosage and Administration section in VASCEPA®'s labeling also instructs clinicians to "[a]dvise patients to swallow VASCEPA capsules whole." *Id.*

250. The Dosage and Administration section in VASCEPA®'s labeling does not specify a duration of use and does not recommend use of any concomitant medication. *Id.*

251. Defendants' proposed labeling includes the same instructions regarding the dose, dosing regimen, and route of administration, and like VASCEPA®'s labeling, does not specify a duration of use or recommend concomitant administration of any other medication. *See* PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596.

C. Dosage Form and Strengths

252. The Dosage Form and Strengths section of a drug label describes the form(s) that the drug product takes and the strength(s) in which the drug product is available.

253. The Dosage Forms and Strengths section of VASCEPA®'s labeling informs clinicians that VASCEPA® is available as a 1-gram or 0.5-gram (500 mg) soft-gelatin capsule. PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

254. The same section in DRL's proposed labeling similarly states that DRL's ANDA Product will be available in 1-gram or 0.5-gram (500 mg) soft-gelatin capsules. PX 574 at 000006–07, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596–97.

255. The Dosage Form and Strengths section of Hikma's proposed labeling states that Hikma's ANDA Product will be available as a 1-gram soft gelatin capsule. *See* PX 274 at 000002, Hikma Proposed Prescribing Information at WWIC0-NV-002836.

D. Contraindications

256. The Contraindications section of a drug label "must describe any situations in which the drug should not be used because the risk of use . . . clearly outweighs any possible therapeutic benefit." 21 C.F.R. § 201.57(c)(5). "Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other indication, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable." *Id.*

257. The Contraindications section of VASCEPA®'s labeling states that VASCEPA® is contraindicated only in patients with known hypersensitivity to VASCEPA® or any of its components. PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

258. Defendants' proposed labeling advises clinicians of the same contraindication. *See* PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000007, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095597.

E. Warnings and Precautions

259. The Warnings and Precautions section of a drug label is intended to describe serious or otherwise clinically significant adverse reactions and safety hazards of which clinicians need to be aware before prescribing the drug. *See* 21 C.F.R. § 201.57(c)(6).

260. The Warnings and Precautions section of VASCEPA®'s labeling encourages clinicians to periodically monitor alanine aminotransferase and aspartate aminotransferase levels in patients with hepatic impairment and to use VASCEPA® with caution in patients with known hypersensitivity to fish and/or shellfish. *See* PX 940 at 000002–03, VASCEPA® Prescribing Information (2017) at AMRN03132169–70.[7]

[7] In VASCEPA®'s new labeling, FDA has removed the hepatic impairment warning, but added warnings noting that, in the REDUCE-IT study, VASCEPA® was associated with an increased risk of atrial fibrillation or atrial flutter and an increased risk of bleeding. *See* PX 1186 at 000002–03, VASCEPA® Prescribing Information (2019) at AMRN03174955–56.

261. Unlike LOVAZA®'s labeling, the Warnings and Precautions section of the VASCEPA® labeling does not warn of a potential increase in LDL-C levels. *Compare* PX 267 at 000003, LOVAZA® Prescribing Information (2010) at AMRN03059152, *with* PX 940 at 000002–03, VASCEPA® Prescribing Information (2017) at AMRN03132169–70.

262. The Warnings and Precautions section of Defendants' proposed labeling includes the same instructions regarding hepatic impairment and allergies as the VASCEPA® labeling and similarly omits any LDL-C warning. *See* PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000007, DRL Proposed Prescribing Information (2018) at DRLEEPA 009559.

F. Description

263. The Description section of a drug label contains "[t]he proprietary name and the established name" of the drug, as well as "[t]he type of dosage form(s) and the route(s) of administration to which the labeling applies." 21 C.F.R. § 201.57(c)(12)(i)(A)–(B).

264. The Description section of the VASCEPA® label states: "VASCEPA®, a lipid-regulating agent, is supplied as either a 0.5-gram or a 1-gram amber-colored, liquid-filled soft gelatin capsule for oral administration." PX 940 at 000004, VASCEPA® Prescribing Information (2017) at AMRN03132171.

265. The Description section of the VASCEPA® label also informs clinicians that the active ingredient in VASCEPA® is "[i]cosapent ethyl," which "is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA)," and that "[e]ach VASCEPA capsule contains . . . 1 gram of icosapent ethyl (in a 1 gram capsule)." *Id.*

266. The Description section of Defendants' proposed labeling similarly describes the form of Defendants' ANDA Products (*i.e.*, soft-gelatin capsules), notes that the drugs are lipid-regulating agents, and instructs clinicians that Defendants' ANDA Products are intended for "oral administration." *See* PX 274 at 000004, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002838 ("Icosapent ethyl, a lipid regulating agent, is supplied as a 1 gram, liquid-filled soft gelatin capsule for oral administration."); PX 574 at 000009, DRL Proposed

Prescribing Information (2018) at DRLEEPA 0095599 ("Icosapent ethyl, a lipid-regulating agent, is supplied as either a 0.5 gram transparent natural colored oval shaped or a 1 gram transparent natural colored oblong shaped, liquid-filled soft gelatin capsule for oral administration").

267. The Description section of Defendants' labeling also informs clinicians that the active ingredient in Defendants' ANDA Products is icosapent ethyl, and that each capsule of Defendants' ANDA Products contains 1 gram of icosapent ethyl. *See* PX 274 at 000004, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002838; PX 574 at 000009, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095599.

G. Clinical Studies

268. The Clinical Studies section of a prescription drug label "must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively." 21 C.F.R. § 201.57(c)(15). "This is usually accomplished by providing concise, accurate summaries of information from studies concerning a drug's effectiveness (and sometimes safety) that practitioners consider important to clinical decision making." PX 776 at 000005, FDA Guidance for Industry: Clinical Studies Section at AMRN-PEXP-0010191.

269. To this end, the Clinical Studies section "must discuss" the "adequate and well-controlled" studies "that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results." 21 C.F.R. § 201.57(c)(15). The "primary objective" is to concisely "summarize (1) the evidence supporting effectiveness in the subjects who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence." PX 776 at 000006, FDA Guidance for Industry: Clinical Studies Section at AMRN-PEXP-001019.

270. The Clinical Studies section should describe the "major design characteristics" of the study, including the "level of blinding," "duration of the study," and the "method of allocation to treatment groups (e.g., randomization)." *Id.* at 000009 It should also describe the

dose and regimen for each study arm and provide "[i]nformation about concomitant therapies . . . to the extent it helps to understand the use of the study drug or its effects." *Id.* at 000009–10.

271. The Clinical Studies section should also identify "those endpoints that establish the effectiveness of the drug" for its approved indication. *Id.* at 000007.

272. Finally, the Clinical Studies section should summarize the study findings, including the "treatment effect" (*i.e.*, the effect that can be attributed to the drug). To do that, FDA recommends that this section describe the "clinical outcome of the treatment relative to the comparator (e.g., placebo or active)." *Id.* at 000010–11.

273. The Clinical Studies section thus instructs clinicians regarding the treatment effect they can expect and intend to achieve when administering the drug per its indicated use.

274. As a result, doctors generally strive to replicate the conditions described in the Clinical Studies section and elsewhere in the label so as to achieve those effects in their patients.

275. The Clinical Studies section of the VASCEPA® labeling describes the design and results of the MARINE study, the primary study that established VASCEPA®'s effectiveness at reducing triglycerides in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. *See* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

276. Defendants' proposed labeling copies the same information concerning the design and results of the MARINE study. *See* PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02.

277. The Clinical Studies section in each label begins by summarizing the major design characteristics of the MARINE study.

14.1 Severe Hypertriglyceridemia

The effects of VASCEPA 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on VASCEPA, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500

> and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74; *see also* PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02.

278. The Clinical Studies section in each label then includes a Table summarizing the "changes in the major lipoprotein lipid parameters" measured in the study.

> The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.
>
> **Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)**

	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence
Parameter	Baseline	% Change	Baseline	% Change	Interval)
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

> % Change= Median Percent Change from Baseline
> Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
> p-values from Wilcoxon rank-sum test
> *p-value < 0.001 (primary efficacy endpoint)
> **p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174; *see also* PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602.

279. Beneath this Table, each label summarizes the results of the study for clinicians with the following conclusion.

> VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174; *see also* PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602.

H. Patient Counseling Information

280. Unlike other sections of the labeling, the Patient Counseling Information section is not intended to inform a physician's prescribing decision. While, "[o]ther sections of the labeling contain the detailed information used by prescribers to fully assess the risks and benefits of a drug for an individual patient," "[t]he intent of [this] section is to identify topics for counseling discussions between health care providers and patients after a prescribing decision has been made." PX 781 at 000006, FDA, *Guidance for Industry: Patient Counseling Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (Dec. 2014) ("FDA Guidance: Patient Counseling Information") at AMRN-PEXP-0010353.

281. The "PATIENT COUNSELING INFORMATION section is written for use by a health care provider to identify topics for a counseling discussion with the patient." *Id.* Accordingly, this section "summarizes the information that health care providers should convey to a patient (or caregiver when applicable) when a counseling discussion is taking place (e.g., a physician prescribing a drug during an office visit…)." *Id.* at 000005.

282. The Patient Counseling Information section "must contain information necessary for patients to use the drug safely and effectively." 21 C.F.R. § 201.57(c)(18). For example, this section must advise physicians to warn patients if "the concomitant use of other substances . . . may have harmful additive effects." *Id.*

283. Sometimes, FDA requires a manufacturer to include in this section information about adverse reactions or drug interactions or "other patient-focused information relevant for providers to convey," such as important instructions on dosing and administration. PX 781 at 000007–11, FDA Guidance: Patient Counseling Information at AMRN-PEXP-0010354-58.

284. The Patient Counseling Information section of the VASCEPA® label recommends that clinicians discuss four topics with patients when prescribing VASCEPA®: (1) VASCEPA® should be used with caution in patients with fish or shellfish allergies; (2) patients should continue diet and exercise while taking VASCEPA®; (3) patients should not alter VASCEPA® capsules and should swallow them whole; and (4) VASCEPA® should be taken exactly as prescribed. *See* PX 940 at 000007–08, VASCEPA® Prescribing Information (2017) at AMRN03132174–75.[8]

285. The Patient Counseling Information section of Defendants' proposed labeling recommends that clinicians discuss the same four topics with patients. *See* PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000013, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095603.

I. Patient Information

286. In addition to the Patient Counseling Information, VASCEPA®'s package insert includes the full text of the FDA-approved "Patient Information" that is directed to patients.

287. Among other things, the Patient Information sheet instructs patients to "[t]ake VASCEPA® exactly as your doctor tells you to take it" and to "not change your dose or stop taking VASCEPA® without talking to your doctor." PX 940 at 000009, VASCEPA® Prescribing Information (2017) at AMRN03132176.

288. The Patient Information also instructs patients to "[t]ake VASCEPA capsules whole" and to "not break, crush, dissolve, or chew VASCEPA capsules before swallowing." *Id.*

[8] The Patient Counseling Information section of the new VASCEPA® labeling instructs clinicians to "[a]dvise the patient to read the FDA-approved patient labeling before starting VASCEPA (Patient Information)," and then lists five topics for discussion with patients: (1) the potential increased risk for atrial fibrillation or atrial flutter; (2) the potential for allergic reactions in patients with hypersensitivity to fish and/or shellfish; (3) the increased risk of bleeding, particularly in patients receiving other antithrombotic agents; (4) the need to swallow VASCEPA® capsules whole, and (5) and the need to take VASCEPA as prescribed. *See* PX 1186 at 000011–12, VASCEPA® Prescribing Information (2019) at AMRN03174964–65.

289. The Patient Information also advises that "your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA®." *Id.*

290. Defendants' proposed Patient Information includes the same instructions to patients as the VASCEPA® Patient Information. *See* PX 274 at 000007–9, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841–43; PX 574 at 000014–16, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095614–06.

XI. INFRINGEMENT LEGAL STANDARDS

291. A patent is infringed where the accused product meets all of the claim limitations, either literally or by equivalence. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989). Determining infringement is a two-step process. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*). First, the court must construe the Asserted Claims, as a matter of law, to ascertain their meaning and scope. *Id.* Second, the trier of fact must compare the properly construed claims against the accused product. *Id.*

292. "Infringement is a question of fact." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). Infringement is proven by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). All probative evidence, including circumstantial evidence, is considered when determining infringement. *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

293. Under 35 U.S.C. § 271(e)(2)(A), the filing of an ANDA pursuant to 21 U.S.C. § 355(j) seeking FDA approval to market a generic form of a drug claimed in a patent "constitutes a technical infringement for jurisdictional purposes." *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). "But the ultimate infringement question" in a Hatch-Waxman case "is determined by traditional patent law principles." *Id.*

294. Because an ANDA applicant has not yet marketed its drug product, the court's infringement analysis involves a "hypothetical inquiry" that focuses "on the product that is likely

to be sold following FDA approval." *Abbotts Labs. v. TorPharm., Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 2002). If the product that the ANDA applicant is asking the FDA to approve falls within the scope of an issued patent claim, a judgment of infringement must necessarily ensue. *Abbotts Labs.*, 300 F.3d at 1373; *Sunovion Pharm.*, 731 F.3d at 1278.

295. Anyone who "actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Establishing inducement requires a patentee to "show that the alleged infringer possessed the requisite intent to induce infringement." *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1334 (Fed. Cir. 2019). To do so, a patentee must show that the alleged infringer (1) "knew or should have known his actions would induce actual infringements," *id.*, and (2) "possessed specific intent to encourage another's infringement," *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 644 (Fed. Cir. 2017).

296. "[W]hile proof of intent is necessary" to show induced infringement, "direct evidence is not required." *Id.* "Circumstantial evidence can support a finding of specific intent to induce infringement." *Vanda Pharm. Inc.*, 887 F.3d at 1129. "[I]nducement can be found where there is [e]vidence of active steps taken to encourage direct infringement, which can in turn be found in advertising an infringing use or instructing how to engage in an infringing use." *Id.* (citation and internal quotation marks omitted).

297. In Hatch-Waxman cases, "[t]he contents of [an ANDA applicant's proposed] label itself may permit the inference of specific intent" to induce infringement. *Id.* In other words, when an ANDA applicant's "proposed label instructs users to perform the patented method," the label itself is "evidence of [the applicant's] affirmative intent to induce infringement." *Id.* A label shows an intent to induce infringement if the label encourages, recommends, promotes, or suggests that clinicians use the generic drug product in a manner that infringes the patent. *Id.*; *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012); *Sanofi*, 875 F.3d at 644; *see also Takeda Pharm. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (active inducement shown when the label "[s]uggests that an

infringing use 'should' be performed"); *Eli Lilly*, 845 F.3d at 1363–64 ("When the alleged inducement relies on a drug label's instructions, the question is . . . whether the instructions teach an infringing use *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent." (internal quotation marks omitted)).

298. Determining what a product label "recommend[s] or suggest[s] to a physician" requires reading the product label from the viewpoint of the clinician. *Bayer*, 676 F.3d at 1324; *see also Vanda*, 887 F.3d at 1131 (citing expert testimony that clinicians read "laboratory tests" in the product label as encouraging clinicians to perform the "genotyping tests" described in the asserted patent claims). In addition, the inducement inquiry is not limited to particular sections of the drug labeling — the court must consider the labeling as a whole. *Bayer*, 676 F.3d at 1324; *See, e.g.*, *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 645–46 (Fed. Cir. 2017) (relying on the Clinical Studies section of the label); *Vanda*, 887 F.3d at 1131 (relying on the Dosage and Administration and Pharmacokinetics sections of the label); *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 585–86 (D. Del. 2018) (Bryson, J.) (relying on the Pharmacokinetics section and "dosing instructions and clinical data" in the product label). It is only when "the label, *taken in its entirety*, fails to recommend or suggest *to a physician* that [the drug] is safe and effective for inducing the claimed combination of effects in patients" is intent to induce infringement lacking. *Bayer* 676 F.3d at 1324 (emphasis added).

299. A patentee need not show that all physicians reading a label will use the generic drug in an infringing manner. Rather, "evidence that the product labeling that Defendants' seek would inevitably lead *some physicians* to infringe establishes the requisite intent for inducement." *Eli Lilly & Co. v. Teva Parenteral Meds.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) (emphasis added); *see also Vanda Pharm. v. West-Ward Pharm.*, 887 F.3d 1117, 1132 (Fed. Cir. 2018) ("Even if not every practitioner will prescribe an infringing dose, that the target dose range 'instructs users to perform the patented method' is sufficient to 'provide evidence of [West-Ward's] affirmative intent to induce infringement.").

XII. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 1 OF THE '728 PATENT.

A. Claim 1 of the '728 Patent

300. Claim 1 of the '728 Patent is an independent claim.

301. Claim 1 of the '728 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

PX 21 at 000021, U.S. Patent No. 8,293,728 at AMRN-PEXP-0000021.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 1 of the '728 Patent

302. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 1 of the '728 Patent that describe the pharmaceutical product that is to be used in this method claim.

303. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

304. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters." Joint Stipulated Facts, ¶¶ 205, 217, 229 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 1

305. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 1 of the '728 Patent.

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "who does not receive concurrent lipid altering therapy"
- "administering orally to the subject about 4 g per day of a pharmaceutical composition"
- "for a period of 12 weeks"
- "to effect a reduction in triglycerides without substantially increasing LDL-C"
- "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy"

See PX 21 at 000021, U.S. Patent No. 8,293,728 at AMRN-PEXP-0000021.

306. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claim 1 of the '728 Patent.

307. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe these remaining limitations in Claim 1 of the '728 Patent for the reasons described below.

1. "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"

308. This limitation requires administration of the claimed pharmaceutical composition to a patient with a fasting baseline TG level between 500 mg/dL and approximately 1500 mg/dL.

309. A clinician who administers Defendants' ANDA products to a patient with a fasting baseline TG level within this range will directly infringe this limitation.

310. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage, Dosage and Administration, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia, *i.e.*, fasting baseline TG levels ≥ 500 mg/dL to about 1500 mg/dL. Moreover, Defendants' experts have not contested that Defendants' labels will encourage clinicians to use Defendants' ANDA Products in "[a] method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl."

a) "triglyceride level of 500 mg/dl to about 1500 mg/dl"

311. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' labeling, like the same section in VASCEPA®'s labeling, states that Defendants' ANDA products will be indicated "as an adjunct to diet to reduce triglycerides (TG) in adult patients with severe (≥500 mg/dL), hypertriglyceridemia" an indication that necessarily includes "subjects having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl" as stated in Claim 1. PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

312. ***Clinical Studies Section.*** In addition, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs physicians that FDA determined that icosapent ethyl 4 g per day effectively reduced triglycerides when administered for twelve weeks to "[p]atients whose baseline TG levels were between 500 and 2,000 mg/dl." PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000007, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

313. Together, these sections of Defendants' proposed labeling instruct clinicians that Defendants' ANDA Products are safe and effective to reduce TGs in patients with TGs ≥ 500 mg/dL.

b) "fasting baseline"

314. ***Dosage and Administration Section.*** The term "baseline," as used to describe a lipid measurement, refers to a measurement done before or at the start of therapy. The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs clinicians to "[a]ssess lipid levels before initiating therapy." PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. That assessment, done before initiating therapy, would establish a "baseline" triglyceride level.

315. ***Clinical Studies Section.*** Additionally, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, specifically states that the triglyceride levels of the patients in the reported study were measured at "baseline." PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

316. It is common practice and well understood by physicians that they must measure patients' lipid levels after the patient has fasted. This is not disputed by the parties.

317. For example, the National Cholesterol Education Program (NCEP) Report of the Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults, also known as the Adult Treatment Panel or ATP III, explains that "[a] lipoprotein profile involving measurement of triglycerides . . . requires a 9- to 12- hour fast." *See* PX 989 at 000091, ATP III at AMRN00290005. The ATP III further explains that "[t]he measurement of any lipid is

preferably performed with the person in a baseline stable condition" otherwise the measurement could "result in values that are not representative of the person's usual level." *Id.*

318. ATP III is a medical guideline that establishes the medical standard of care for clinicians treating patients with elevated lipids. *See generally* PX 989, ATP III. The treatment guidelines in the ATP III are common knowledge among clinicians who treat these patients.

319. Thus, when Defendants' labeling, like VASCEPA®'s labeling, instructs clinicians to "[a]ssess lipid levels before initiating therapy," and to administer Defendants' generics to patients with TG ≥ 500 mg/dL, clinicians will understand the labeling to be referring to patients' *fasting* baseline TG levels. *See* PX 274 at 000001–02, 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835–36, WWIC0-NV-002840–41; PX 574 at 000006, 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596, DRLEEPA 0095601–02; PX 940 at 000002, 000006–07, Vascepa® Prescribing Information (2017) at AMRN03132169, 3132173–74.

320. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—according to "[a] method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," as required by Claim 1 of the '728 Patent.

2. "who does not receive concurrent lipid altering therapy"

321. This limitation requires administration of the claimed pharmaceutical composition to a patient who is not on a "concurrent lipid altering therapy." The Court previously construed the term "concurrent lipid altering therapy" to mean "a medication to alter lipid levels in a subject whereby the medication is administered concurrently / concomitantly with the administration of a pharmaceutical composition comprising ethyl eicosapentaenoate." Claim Construction Order at 5–7 (ECF No. 135). Statins are a prototypical example of a "medication to alter lipid levels."

322. Based on the Court's construction, a clinician who administers Defendants' ANDA Products to a patient who is not on another lipid altering medication (*e.g.*, a statin) will directly infringe this limitation.

323. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage, Dosage and Administration, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia who do not receive concurrent lipid altering therapy.

324. ***Indications and Usage Section.*** Specifically, the Indications and Usage section of Defendants' labeling, like the same section in VASCEPA®'s labeling, states that Defendants' ANDA products will be indicated "as an adjunct to diet to reduce triglycerides (TG) in adult patients with severe (≥500 mg/dL)." PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. The Indications and Usage section does not require or otherwise reference the use of any other medication with Defendants' ANDA Products. The Indications and Usage section thus instructs the use of Defendants' ANDA Products as a mono-pharmacotherapy, without coadministration of any other drug.

325. If a drug is approved *only* for use in combination with another therapy or therapeutic modality, FDA requires an applicant to include a statement to that effect in the Indications and Usage section of the drug's label. *See* PX 573 at 000007, 000012, FDA Guidance for Industry: Indications and Usage at AMRN-PEXP-0010251, AMRN-PEXP-0010253.

326. Without a statement referring to another medication in the indication, a clinician reading Defendants' labeling will understand that FDA has determined that Defendants' ANDA products, when used in combination with diet, are safe and effective to reduce TGs in adult

patients with severe hypertriglyceridemia without coadministration of any other medication, including any lipid-altering therapy like statins.

327. ***Dosage and Administration Section.*** This encouragement is reinforced by the Dosage and Administration sections of Defendants' proposed labeling. When FDA has determined that a drug should be used with another drug to "minimize toxicity" or "enhance effectiveness," or "if [a] drug has been demonstrated to be effective only in combination with another therapy," the Dosage and Administration section of the drug's label "should identify and describe any recommended concomitant medications" or "therap[ies]." PX 572 at 000008, FDA Guidance for Industry: Dosage and Administration Section (2010) at AMRN-PEXP-0010236.

328. But the Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, does not "identify" or "describe" any "recommended concomitant medications." *See* PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. Because Defendants seek approval of their ANDA products for use as an "adjunct to diet," the Dosage and Administration sections advise clinicians that "[p]atients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl, which should continue during treatment with icosapent ethyl." PX 274 at 000001–02, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835–36; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. By not mentioning any premedication regimen or any concomitant drug therapy, a clinician will read Defendants' labeling and understand that the safety and effectiveness of Defendants' ANDA Products, when administered to reduce TGs in adult patients with severe hypertriglyceridemia, does not require coadministration of any other drug, including other lipid altering medications.

329. ***Clinical Studies Section.*** The Clinical Studies section of Defendants' proposed labeling, like the same section in VASCEPA®'s labeling, further encourages clinicians that a

concurrent lipid altering therapy is not needed when they administer Defendants' ANDA Products. Under FDA regulations, "the Clinical Studies section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively." PX 776 at 000005, FDA Guidance for Industry: Clinical Studies Section (Jan. 2006) at AMRN-PEXP-0010190.

> This is usually accomplished by providing concise, accurate summaries of information from studies concerning a drug's effectiveness (and sometimes safety) that practitioners consider important to clinical decisionmaking." *Id.* To help clinicians under the results of any reported study, the Clinical Studies section describes the study design, including by providing "[i]nformation about concomitant therapies . . . to the extent it helps to understand the use of the study drug or its effects.

Id. at 000006–07.

330. The Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, describes the results of a double-blind, placebo-controlled study in which 4 g of icosapent ethyl was administered for 12 weeks to patients with baseline TG levels between 500 and 2,000 mg/dL. In describing this study, the Clinical Studies section specifically notes that only "[t]wenty-five percent of patients" in the study "were on concomitant statin therapy." PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74. When reviewing Defendants' proposed labeling, clinicians will immediately appreciate that the remaining 75% of the patients in the study described in the Clinical Studies section were not on concurrent lipid altering therapy (e.g., statins). Clinicians understand this to instruct them that the clinical study included subjects who were on concurrent statin therapy and even more patients who were not on concurrent statin therapy, but was approved for use without any concomitant medication (including statins) because FDA did not believe the effectiveness (or safety) of icosapent ethyl in reducing TGs in adult patients with severe hypertriglyceridemia was dependent on concomitant statin therapy.

331. Furthermore, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs physicians that, when administered to adult patients with severe hypertriglyceridemia, 4 g per day of icosapent ethyl reduced patients' TG levels while reducing VLDL-C and apoB and without raising LDL-C. PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74. This further instructs clinicians that they may administer Defendants' ANDA Products to adult patients with severe hypertriglyceridemia without causing adverse effects in the patients' other major lipoprotein lipid levels that would require coadministration of another lipid-altering medication (*e.g.*, statins) to treat or manage.

332. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice will be used—by patients who "do[] not receive concurrent lipid altering therapy" as required by Claim 1 of the '728 Patent.

3. "administering orally to the subject about 4 g per day of a pharmaceutical composition"

333. This limitation requires oral administration to patients of about 4 g, or 4 grams, per day of the claimed pharmaceutical composition.

334. As an initial matter, Defendants' experts have not contested that Defendants' labels will encourage clinicians to use Defendants' ANDA Products by "administering orally to the subject about 4 g per day of [the] pharmaceutical composition" described in the Asserted Claims.

a) "administering orally"

335. The court previously interpreted the term "administering orally" as "the doctor prescribing the medication, and the medication is delivered into the patient's body at the doctor's direction." Claim Construction Order, at 8 (ECF No. 135).

336. The Court's claim construction recognizes that Defendants' ANDA Products are available only with a prescription from a clinician. Any administration of the medication is impossible without the clinician prescribing the medication for and providing instructions to the patient, and all administration of Defendants' ANDA Products is therefore done under the direction of a clinician.

337. Consistent with the Court's construction, a clinician who prescribes Defendants' ANDA products and directs a patient to orally deliver the medication into the body will directly infringe this limitation.

338. Defendants will induce infringement of this limitation because clinicians will read the Description, Dosage and Administration, Patient Counseling Information, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting clinicians to prescribe 4 g of Defendants' ANDA products to patients and to direct the patients to take the 4 g per day orally.

339. ***Description Section.*** Specifically, the Description section of Defendants' labeling, like the same section in VASCEPA®'s labeling, states that Defendants' ANDA Products are "1-gram . . . soft gelatin capsule[s] for oral administration." PX 274 at 000004, Hikma Proposed Prescribing Information (2018) at WWIC0-NV-002838; PX 574 at 000009, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095599; *see also* PX 940 at 000004, VASCEPA® Prescribing Information (2017) at AMRN03132171.

340. ***Dosage and Administration Section.*** In addition, the Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, states that "[p]atients should be advised to swallow icosapent ethyl capsules whole." PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 00002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

341. ***Patient Counseling Information Section.*** The Patient Counseling Information section of Defendants' labeling, like the same section in VASCEPA®'s labeling, further

encourages clinicians to "advise[]" patients to "not alter [Defendants'] capsules in any way and to ingest intact capsules only" and "[i]nstruct patients to take [Defendants' ANDA Products] as prescribed." PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000013, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095603; *see also* PX 940 at 000007–08, VASCEPA® Prescribing Information (2017) at AMRN03132174–75. By communicating to clinicians that they should instruct their patients to swallow the capsules whole, Defendants' labeling instructs, advises, and encourages physicians to prescribe Hikma's ANDA Product to their patients and then direct the patients on the manner in which the medication should be delivered into their bodies—orally.

342. Patients will orally ingest the medication according to their clinician's instructions. The Patient Information sheet associated with Defendants' labeling, like the Patient Information sheet associated with VASCEPA®'s labeling, which is directed to patients themselves, instructs patients to "[t]ake icosapent ethyl capsules exactly as your doctor tells you to take it," to "[t]ake icosapent ethyl capsules whole," and to "not break, crush, dissolve, or chew icosapent ethyl capsules before swallowing." PX 274 at 000008, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002842; PX 574 at 000015, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095605; *see also* PX 940 at 000009, VASCEPA® Prescribing Information (2017) at AMRN03132176. Defendants' labeling thus directs patients to follow their clinician's instructions on how to take Defendants' ANDA Products and to ingest the capsules orally.

343. Thus, Defendants' labeling instructs physicians to direct their patients how to deliver the drugs into their bodies, and encourages patients to follow through on those instructions, as required by the court's construction of "administering orally."

b) "about 4 g per day of a pharmaceutical composition"

344. Defendants' labeling further instructs and encourages clinicians to prescribe and direct their patients to take "about 4 g per day."

345. The parties have agreed that the term "about" as used in the Asserted Claims means "approximately." Agreed Constructions of the Claim Terms, ECF No. 83-2 at 4. This limitation thus requires administration of "approximately" 4 g per day of the pharmaceutical composition.

346. The parties also have agreed that the term "pharmaceutical composition" as used in the Asserted Claims means "a composition suitable for inclusion in a dosage form for administration to patients." *See* Plaintiffs' Proposed Constructions of the Claim Terms, ECF No. 83-3 at 5–6; Tr. of Markman Hearing at 6:15–7:4 (confirming parties' agreement to Plaintiffs' proposed construction of "pharmaceutical composition"). In other words, the term "pharmaceutical composition" refers to the drug substance inside of Defendants' ANDA Products.

347. It is uncontested that Defendants' ANDA Products are 1-gram soft-gelatin capsule. Joint Stipulated Facts ¶¶ 213, 225 (ECF No. 324). The 1-gram strength refers to the approximate weight of the drug substance (*i.e.*, pharmaceutical composition) inside the capsule.

348. ***Dosage and Administration Section.*** The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs that the daily dose of Defendants' 1-gram icosapent ethyl capsules is 4 grams per day taken as 2 capsules twice daily with food. PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. A daily dose of Defendants' ANDA Products will thus comprise 4 1-gram capsules, which will contain approximately 4 g of drug substance (*i.e.*, pharmaceutical composition).

349. ***Description Section.*** The Description section of DRL's proposed labeling, like the same section in VASCEPA®'s labeling, expressly states that each icosapent ethyl (or VASCEPA®) capsule "contains . . . 1 gram of icosapent ethyl (in a 1 gram capsule)." PX 574 at 000009, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095599; PX 940 at

000004, VASCEPA® Prescribing Information (2017) at AMRN03132171. Meanwhile, the Description section of Hikma's proposed labeling confirms that its ANDA Product supplies "[i]cosapent ethyl . . . as a 1 gram . . . capsule." PX 274 at 000004, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002838.

350. ***Clinical Studies Section.*** Additionally, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs clinicians that "icosapent ethyl 4 grams per day" was effective to reduce TGs (while also reducing apoB and without increasing LDL-C). PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 11–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

351. Defendants' labeling thus encourages, promotes, recommends, or suggests administration of approximately 4 g per day of the claimed pharmaceutical composition.

* * *

352. Accordingly, use of Defendants' ANDA Product in accordance with the advice, instructions, and encouragement in Defendants' proposed prescribing information will, if approved, meet the "administering orally to the subject about 4 g per day of a pharmaceutical composition" limitation, as interpreted through the court's construction of "administering orally" and the parties' agreed constructions of "about" and "pharmaceutical composition."

353. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be—and in clinical practice will be—"administer[ed] orally to the subject about 4 g per day of a pharmaceutical composition" as required by Claim 1 of the '728 Patent.

4. "for a period of 12 weeks"

354. This limitation requires administration of the claimed pharmaceutical composition for at least 12 weeks.

355. A clinician who administers Defendants' ANDA Products for at least 12 weeks will directly infringe this limitation.

356. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage, Dosage and Administration, Clinical Studies, and Patient Counseling sections of Defendants' labeling as instructing the use of Defendants' ANDA products as chronic therapy for a chronic condition. Defendants' labeling therefore encourages, recommends, or instructs administration of Defendants' ANDA products for at least 12 weeks.

357. As an initial matter, clinicians will read Defendants' labeling with the understanding that severe hypertriglyceridemia is almost invariably a chronic condition requiring long-term drug therapy. *See supra* ¶¶ 119–21.

358. Indeed, when FDA approved VASCEPA®, the RLD for Defendants' ANDA Products, to reduce TG levels in adult patients with severe hypertriglyceridemia, the same indication for which Defendants seek approval, FDA approved VASCEPA® for a chronic use indication. Accordingly, if approved, Defendants' ANDA Products will also be approved for a chronic use indication.

359. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' labeling, like the same section in VASCEPA®'s labeling, states that Defendants' ANDA Products are "indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132168–69.

360. Additionally, the Indications and Usage section of Defendants' labeling, like the same section in VASCEPA®'s labeling, lacks any limited duration of administration. *See* PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835–36; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

361. Because clinicians already know that severe hypertriglyceridemia is a chronic condition, the fact that the Indications and Usage section does not limit the duration of use of Defendants' ANDA Products instructs or encourages clinicians to prescribe Defendants' ANDA Product for long-term therapy, and thus for at least 12 weeks. *See supra* ¶¶ 119–21.

362. Furthermore, clinicians will understand that, if FDA had approved Defendants' ANDA Products (or VASCEPA®) for only short-term use—perhaps because the drugs are intended to treat a short-term condition, because their risk-benefit profile changes adversely with continued use, or because they are thought to lose effectiveness after a certain duration of use—the labeling would expressly communicate that fact.

363. When a drug is approved only for a particular duration of use, FDA requires the labeling communicate the duration of use to prescribers. For example, FDA guidance on the format and content of the Indications and Usage section of prescription drug labels states:

> [i]f information on limitations of use or uncertainty about anticipated benefits is relevant . . . to appropriate treatment duration when treatment should be limited, . .. the INDICATIONS AND USAGE section 'must . . . include a concise description of the information, with a reference to the more detailed information in the "Dosage and Administration" section' (§ 201.57(c)(2)(i)(D)). Under these circumstances, information about important dose or duration considerations, such as how long a drug can safely be used or uncertainty about the risks and benefits of treatment beyond a certain period (e.g., long-term cumulative toxicity), should be included as a limitation of use.

PX 573 at 000015, FDA Guidance for Industry: Indications and Usage Section at AMRN-PEXP-0010256.

364. The guidance goes on to say that "[i]t is generally not necessary to limit duration of use in the INDICATIONS AND USAGE section unless such a limited duration is essential to safe and effective use of the drug." *Id.* at 000016

365. FDA guidance also advises against specifying a duration of use in the Indications and Usage section of a label for drugs that, while studied in short-term clinical trials, are

approved for "long-term use due to the chronic nature of the condition and because there is no known or anticipated safety or efficacy concern from continued use." *Id.*

366. Additionally, the Indications and Usage section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs clinicians that "[p]atients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving icosapent ethyl capsules and should continue this diet and exercise regimen with icosapent ethyl capsules." PX 274 at 00001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

367. This section of Defendants' labeling, like the same section in VASCEPA®'s labeling, further instructs clinicians that "[a]ttempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy." PX 274 at 000001, Hikma Proposed Prescribing Information at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

368. Clinicians understand this language to instruct or encourage them to rule out transient causes of severe hypertriglyceridemia before administering VASCEPA® or Defendants' proposed ANDA Products. In doing so, clinicians can be sure that their patients' severe hypertriglyceridemia is chronic.

369. Given that the Indications and Usage section indicates Defendants' ANDA products for a chronic condition, does not limit the duration of use, and instructs clinicians to rule out any transient causes of severe hypertriglyceridemia in their patients, clinicians will read this section of the label to instruct or encourage them to administer for at least 12 weeks.

370. ***Dosage and Administration Section.*** The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, does not specify any duration of use. *See* PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

371. As with the Indications and Usage section, clinicians understand the lack of a limited duration in the Dosage and Administration section to instruct or encourage them to administer Defendants' ANDA products (or VASCEPA®) for at least 12 weeks. Clinicians understand that the drug is used to treat a chronic condition. Clinicians further understand that if the drug were safe and effective for only a limited duration of time, the Dosage and Administration section would include such a duration.

372. Under FDA guidance, the Dosage and Administration section of a drug label must specify the approved "[d]uration of use, *when duration should be limited* (e.g., because of lack of data on long-term use and a basis for concern about toxicity associated with long-term use, cumulative toxicity, or tolerance)." PX 572 at 00005, FDA Guidance for Industry: Dosage and Administration Section at AMRN-PEXP-0010233 (emphasis added). This section also must identify the approved duration of use "[i]f it is known that a drug provides no additional benefit . . . beyond a certain duration of use," or "[i]f it is known that . . . beyond a certain duration of use, toxicity is increased to an extent that the risk exceeds the benefit." *Id.*

373. By omitting any duration of use, the Dosage and Administration section of Defendants' labeling instructs clinicians that Defendants' ANDA Products, if approved, will be indicated for long-term use for a chronic condition, and that there is no known safety or efficacy concern that requires a short-term duration of use.

374. ***Clinical Studies Section.*** The Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, reports the results of the primary clinical study that established the effectiveness of icosapent ethyl 4 g per day in treating patients with severe

hypertriglyceridemia. When describing the important details of the study, this section of the labeling expressly states that patients were administered icosapent ethyl 4 g per day "for 12 weeks." PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000011, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

375. The Clinical Studies section further contains only the effects on the patients' TGs and other lipid levels after 12 weeks of administration; no other data is available to clinicians in the labels. In particular, the Clinical Studies section reports that after administration of the medication for 12 weeks, the patients' TG levels were reduced by 27% compared to baseline and by 33% compared to placebo. PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

376. By reporting that 4 g per day of icosapent ethyl is effective after 12 weeks of administration, Defendants' labels, like the VASCEPA® label, encourage clinicians to administer Defendants' ANDA Products for at least 12 weeks. The labels therefore instruct clinicians that, to have a similar treatment effect in their patients, they should administer Defendants' ANDA Products for at least 12 weeks.

377. Moreover, FDA explains that the goal of the Clinical Studies section is to recommend or encourage the safe and effective use of the product by describing both the conditions under which the drug has been found safe and effective and the expected treatment effects. *See generally* PX 776 at 000005–12, FDA Guidance for Industry: Clinical Studies Section (2006) at AMRN-PEXP-0010191–98.

378. The Clinical Studies section of Defendants' labeling, if approved, will thus instruct clinicians that Defendants' ANDA Products are approved for long-term administration,

and that clinicians should administer Defendants' ANDA Products for at least 12 weeks to obtain the treatment effect described in the labeling.

379. ***Patient Counseling Information Section.*** The Patient Counseling Information section of Defendants' labeling, like the same section in VASCEPA®'s labeling, advises clinicians to "[i]nstruct patients to take icosapent ethyl as prescribed." PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000013, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095603; *see also* PX 940 at 00007–08, VASCEPA® Prescribing Information (2017) at AMRN03132174–75. Clinicians understand this section to be recommending and encourage them to direct their patients to take Defendants' ANDA Products (or VASCEPA®) for as long as the clinician prescribes it.

380. Moreover, FDA regulations require that drug labels include a Patient Counseling Information section that "contain[s] information necessary for patients to use the drug safely and effectively." 21 C.F.R. § 201.57(c)(18). The Patient Counseling Information section is intended to "summarize[] the information that a health care provider should convey to a patient (or caregiver when applicable) when a counseling discussion is taking place (e.g., a physician prescribing a drug during an office visit . . .)." PX 781 at 000005, FDA Guidance for Industry: Patient Counseling Information Section (2014) at AMRN-PEXP-0010352.

381. Thus, FDA's regulations further confirm that the Patient Counseling Information section of Defendants' proposed labeling, if approved will instruct patients to take Defendants' ANDA products for as long as their clinician prescribes it.

382. ***Patient Information.*** The Patient Information that is associated with Defendants' labeling, like the Patient Information that is associated with the VASCEPA® labeling, is directed to patients, and specifically instructs patients to "[t]ake icosapent ethyl exactly as your doctor tells you to take it" and to "not change your dose or stop taking icosapent ethyl without talking to your doctor." PX 274 at 000008, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002842; PX 574 at 000015, DRL Proposed Prescribing Information (2018) at DRLEEPA

0095605; *see also* PX 940 at 000009, VASCEPA® Prescribing Information (2017) at AMRN03132176.

383. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be—and in clinical practice they will be—administered "for a period of 12 weeks" as required by Claim 1 of the '728 Patent.

5. "to effect a reduction in triglycerides without substantially increasing LDL-C"

384. This limitation requires administration of the claimed pharmaceutical composition "to effect a reduction in triglycerides without substantially increasing LDL-C."

385. The Court construed the term "to effect" as referring to the intended result of the claimed method of treatment and further requiring that the intended result actually occur. Claim Construction Order, at 11 (ECF No. 135) ("[I]n other words, the patent requires that the intended effect actually occur.").

386. A clinician who administers Defendants' ANDA Products and intends to and does cause these lipid effects will directly infringe this limitation.

387. Defendants' will induce infringement of this limitation because clinicians will read the Indications and Usage, Clinical Studies, and Warnings and Precautions sections of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to reduce TGs without substantially increasing LDL-C, and instructs physicians that such effects will in fact occur in most patients.

a) "to effect a reduction in triglycerides"

388. As an initial matter, Defendants' experts have not contested that Defendants' labels will encourage clinicians to use Defendants' ANDA Products "to effect a reduction in triglycerides."

389. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' labeling, like the same section in the VASCEPA® labeling, states that Defendants' ANDA Products are "indicated . . . to reduce triglyceride (TG) levels in adult patients with

severe (≥500 mg/dl) hypertriglyceridemia." PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169.

390. ***Clinical Studies Section.*** In addition, the Clinical Studies section in Defendants' labeling, like the same section in the VASCEPA® labeling, instructs clinicians that Defendants' ANDA Products (like VASCEPA®) have been shown to be effective at reducing TGs in adult patients with severe hypertriglyceridemia. Specifically, the Clinical Studies section shows that the TG levels of patients receiving 4 g per day of icosapent ethyl for 12 weeks experienced a 27% reduction in TGs from baseline and a 33% reduction compared to placebo. The Clinical Studies section then specifically highlights for clinicians that "[i]cosapent ethyl 4 grams per day reduced median TG [triglycerides] . . . from baseline relative to placebo." PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74). By demonstrating the known treatment effect of icosapent ethyl 4 g per day when administered for 12 weeks, the Clinical Studies section of Defendant's labeling (like the VASCEPA® labeling) encourages clinicians to administer Defendants' ANDA Products to treat their severely hypertriglyceridemic patients with the intent to reduce their triglycerides. The clinical study results further demonstrate that such a reduction in triglycerides will in fact occur in a majority of such patients.

391. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in triglycerides" as required by Claim 1 of the '728 Patent.

b) "without substantially increasing LDL-C"

392. The Court previously construed the term "without substantially increasing LDL-C" to mean "without a clinically meaningful increase in LDL-C." Claim Construction Order, at 9–10 (ECF No. 135).

393. In the context of the patents at issue, a "clinically meaningful increase in LDL-C" is an increase of about 5% of greater. For example, the so-called "rule of 6%" is well known among physicians treating patients with elevated lipids; a 6% rise in LDL will cause a physician to evaluate the patient's current treatment regimen—out of concern for the patient's cardiovascular risk—and for example may result in the physician doubling the patient's current statin dosage. *See* PX 989 at 000184, ATP III, at AMRN00290098 ("[T]he dose of a statin may be doubled at each visit to achieve an additional 6–7 percent LDL lowering with each dose titration.").

394. Defendants will induce infringement of this portion of the claim because clinicians will read the Clinical Studies, Dosage and Administration, and Warnings and Precautions sections of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to reduce TGs in a severely hypertriglyceridemic patient without substantially increasing a patient's LDL-C levels, and Defendants' labeling demonstrates that such effects will in fact occur in most patients.

395. ***Dosage and Administration Section.*** The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs clinicians to "[a]ssess lipid levels before initiating therapy." PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. Thus, Defendants' proposed labeling advises clinicians that the patient's entire lipid panel—including the patient's LDL-C levels—is an important consideration for clinicians when treating severe hypertriglyceridemia.

396. ***Clinical Studies Section.*** The Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, expressly instructs clinicians that "[t]he reduction in TG [triglycerides] observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." In addition, Table 2 in the Clinical Studies section reports that patients experienced a 5% reduction in LDL-C compared to baseline and a 2% reduction in LDL-C compared to placebo. PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41. PX 574 at 0000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

397. ***Warnings and Precautions Section.*** The Warnings and Precautions section in Defendants' labeling, like the same section in VASCEPA®'s labeling, omits any warning that patients' LDL-C levels may rise as a result of treatment. The absence of this warning would be conspicuous to clinicians and encourage further investigation into the effects of icosapent ethyl on severely hypertriglyceridemic patients' LDL-C levels because the prescribing information for LOVAZA®, a medication used to treat severe hypertriglyceridemia before icosapent ethyl, and several fibrates, contained such a warning. For example, the 2007 version of the LOVAZA® label stated in the "Precautions" section that "[i]n some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels." PX 566 at 000001, LOVAZA® Label (2007) at AMRN01187779. The label further instructed clinicians that "LDL-C levels should be monitored periodically during Lovaza therapy." *Id.*; *see also, e.g.*, PX 267 at 000001, 000003, Lovaza® Prescribing Information (Dec. 2010) at AMRN0305915051 ("LOVAZA may increase levels of LDL. Monitor LDL levels periodically during therapy."); *id.* at 000003 ("In some patients, LOVAZA increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with LOVAZA.").

398. Additionally, as described above (*see supra* § VII.E.3) the labels of several fibrates warn of a rise in LDL-C. *See* PX 964 at 000002, LOPID® PDR 1990 at AMRN-PEXP-0001612 ("Patients with significantly elevated triglycerides should be closely observed when

treated with gemfibrozil. In some patients with high triglycerides levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol."); *see also* PX 825 at 000003, LOPID® PDR 2004 at 2556 (same); PX 966 at 000004, TRICOR® PDR I at 529, Table 2 at AMRN-PEXP-0001936) (reporting that in patients with TG levels from 500 to 1500 mg/dL, LDL-C increased by 45% from baseline in individuals using TRICOR, with a placebo-adjusted increase of 49.2%); PX 937 at 27, TRILIPIX® Label 2008 at 27 (AMRN01598415) ("Treatment of patients with elevated TG often results in an increase of LDL-C (Table 7)."); *id.* at Table 7 (reporting 45% increase in LDL-C from baseline with a placebo-adjusted increase in LDL-C of 49.2%).

399. Together, these sections of Defendants' labeling encourage, recommend, promote, or suggest clinicians administer Defendants' ANDA Products, with the intent to reduce patients' TG levels without substantially increasing LDL-C, with the expectation that those results will in fact be achieved. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

400. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"without substantially increasing LDL-C" as required by Claim 1 of the '728 Patent.

6. "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy"

401. The Court construed the term "compared to" to have its plain and ordinary meaning. Ultimately, this term simply refers to "a comparison between what happens when the treatment is administered versus what would otherwise happen to a second subject" who does not receive treatment. Claim Construction Order, at 12–13 (ECF No. 135). This term "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects" and "the clinical data in the [patent file history] . . . supports . . . the term's plain and ordinary meaning." *Id.* at 13 (ECF No. 135).

402. The "compared to" claim language is linked to the "to effect" claim language. The "to effect" limitation requires that the effect actually occur and the "compared to" limitation instructs how to determine that the claimed effect has occurred.

403. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia to reduce the patients' TG levels without substantially increasing LDL-C "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dL to about 1500 md/dL who has not received the pharmaceutical composition and a concurrent lipid altering therapy."

404. ***Clinical Studies Section.*** As noted previously, the Clinical Studies section in Defendants' labeling, like the same section in VASCEPA®'s labeling, reports the results of a placebo-controlled study in which investigators administered 4 g per day of icosapent ethyl to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo (*i.e.*, a product with no active ingredient (no icosapent ethyl) to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Thus, during the course of the study these 75 subjects did not receive the "pharmaceutical composition" described in Claim 1 of the '728 Patent—96% EPA and substantially no DHA. *See* PX 274 at 6, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602. And many of these subjects also did not receive "a concurrent lipid altering therapy" as required by Claim 1 of the '728 Patent. PX 274 at 6, Hikma Proposed Prescribing Information (2016) (WWIC0-NV-002840) (providing that 75% of the subjects in the study were not on concurrent statin therapy); PX 574 at 11–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02 (same). Accordingly, the placebo group consists of "second subject[s] having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who have not received the pharmaceutical composition and a concurrent lipid altering therapy," as provided in Claim 1.

405. Table 2 in the Clinical Studies section of Defendants' labeling, like Table 2 in the Clinical Studies section of VASCEPA®'s labeling, reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received icosapent ethyl, compared to baseline and compared to placebo. This information provides a comparison of the lipid effects experienced by this group of "second subject[s]" to the lipid effects experienced the group who received the icosapent ethyl treatment. *See* PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

406. The label instructs clinicians on the degree to which icosapent ethyl beneficially alters lipid levels in patients with severe hypertriglyceridemia from their pre-treatment levels. Defendants' labeling thereby encourages clinicians to administer Defendants' ANDA Products to severely hypertriglyceridemic patients with the intent to cause these beneficial lipid effects. Furthermore, the labeling demonstrates that such effects will in fact occur in such patients.

407. As relevant to this limitation, Table 2 instructs clinicians that patients who were administered icosapent ethyl experienced a median 27% reduction in TG levels from baseline and a median 5% reduction in LDL-C levels from baseline, while patients in the placebo group experienced a median 10% increase in TG levels from baseline and a median 3% reduction in LDL-C compared to baseline. Critically, Table 2 further instructs clinicians that the administration of icosapent ethyl 4 g per day for 12 weeks caused a median 33% reduction in TGs and a median 2% reduction in LDL-C when compared to placebo control (*i.e.*, compared to the 75 patients who did not receive the treatment). Furthermore, the TG reduction from baseline relative to placebo was statistically significant. While the LDL-C reduction compared to placebo was not statistically significant, median LDL-C levels also did not increase, let alone increase substantially.

Table 2: Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	Icosapent Ethyl 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33[1] (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29[2] (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9[2] (-14, -3)

% Change = Median Percent Change from Baseline
Difference = Median of [Icosapent Ethyl % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test
1. p-value < 0.001 (primary efficacy endpoint)
2. p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

PX 274 at 6, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; *see also* PX 574 at 12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 7, VASCEPA® Prescribing Information (2017) at AMRN03132174.

408. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that icosapent ethyl 4 g per day reduced TGs from baseline relative to placebo in severely hypertriglyceridemic patients.

> Icosapent ethyl 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo.

PX 274 at 000007, Hikma Prescribing Information (2016) at WWIC0-NV-002841; *see also* PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

409. The Clinical Studies section of Defendants' labeling (and VASCEPA®'s labeling) thus instructs clinicians that icosapent ethyl 4 g per day reduces TGs without substantially raising LDL-C compared to placebo control when administered for 12 weeks, and thereby encourages clinicians to administer Defendants' ANDA Products with the intent to reduce TGs in their severely hypertriglyceridemic patients while having the additional beneficial effect of not substantially raising those patients' LDL-C levels (compared to what they would have been with

no treatment). Furthermore the Clinical Studies section demonstrates that clinicians will in fact observe such results in their patients.

410. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—to effect a reduction in triglycerides without substantially increasing LDL-C "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy," as required by Claim 1 of the '728 Patent.

* * *

411. Clinicians will thus perform each of the method steps in Claim 1 of the '728 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XIII. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 16 OF THE '728 PATENT.

A. Claim 16 of the '728 Patent

412. Claim 16 of the '728 Patent is a dependent claim that depends from Claim 1 of the '728 Patent.

413. As a dependent claim, Claim 16 incorporates the limitations in Claim 1.

414. Claim 1 of the '728 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

PX 21 at 000021, U.S. Patent No. 8,293,728 at AMRN-PEXP-0000021.

415. Claim 16 of the '728 Patent recites:

> The method of claim 1, wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined.

PX 21 at 000022, U.S. Patent No. 8,293,728 at AMRN-PEXP-0000022.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 16 of the '728 Patent

416. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 16 of the '728 Patent that describe the pharmaceutical product that is to be used in this method claim.

417. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

418. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters." Joint Stipulated Facts, ¶¶ 205, 217, 229 (ECF No. 324).

419. Third, Defendants have stipulated that their ANDA Products, as well as VASCEPA®, contain a "pharmaceutical composition" "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined." Joint Stipulated Facts ¶¶ 206, 218, 230 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 16

420. As a dependent claim, Claim 16 of the '728 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '728 Patent.

421. For the reasons discussed at Paragraphs 300–411 above, Defendants will induce infringement of all limitations in Claim 1 of the '728 Patent.

422. As noted above, Defendants have stipulated that their ANDA Products will meet the only limitation that Claim 16 adds to Claim 1. *See supra* ¶¶ 417–19.

423. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—as required by Claim 16 of the '728 Patent.

* * *

424. Clinicians will perform each of the method steps in Claim 16 of the '728 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XIV. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 14 OF THE '715 PATENT.

A. Claim 14 of the '715 Patent

425. Claim 14 of the '715 Patent is a dependent claim that depends from Claim 13 of the '715 Patent.

426. As a dependent claim, Claim 14 incorporates the limitations in Claim 13.

427. Claim 13 of the '715 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject.

PX 22 at 000022, U.S. Patent No. 8,318,715 & Certificate of Correction at AMRN-PEXP-0000044.

428. Claim 14 of the '715 Patent recites:

> The method of claim 13 comprising administering to the subject about 4 g per day of the pharmaceutical composition to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of [LDL-C] in the subject.

PX 22 at 000022–23, U.S. Patent No. 8,318,715 & Certificate of Correction at AMRN-PEXP-0000044–45.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 14 of the '715 Patent

429. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claims 14 of the '715 Patent (which depends from Claim 13) that describe the pharmaceutical product that is to be used in this method claim.

430. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

431. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters." Joint Stipulated Facts, ¶¶ 207, 219, 231 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 14

432. As a dependent claim, Claim 14 of the '715 Patent incorporates the limitations of the claim from which it depends, Claim 13 of the '715 Patent.

433. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 14 of the '715 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "who does not receive a concurrent lipid altering therapy"
- "administering orally to the subject about 4 g per day of a pharmaceutical composition"
- " for a period of at least 12 weeks"
- " to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of [LDL-C] in the subject"

See PX 22 at 000022–23, U.S. Patent No. 8,318,715 & Certificate of Correction at AMRN-PEXP-0000044–45.

434. As discussed above, Defendants will induce direct infringement of the following disputed limitations in Claim 14 of the '715 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," *see supra* ¶¶ 308–20;
- "who does not receive a concurrent lipid altering therapy," *see supra* ¶¶ 321–32;[9] and
- "administering orally to the subject about 4 g per day of a pharmaceutical composition," *see supra* ¶¶ 333–53.

435. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claims 14 of the '715 Patent:

- "for a period of at least 12 weeks"
- "to effect a statistically significant reduction in triglycerides and apolipoprotein B without effect a statistically significant increase of [LDL-C] in the subject"

436. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 14 of the '715 Patent for the reasons described below.

1. "for a period of at least 12 weeks"

437. Claim 14 of the '715 Patent, by virtue of its dependence from Claim 13, requires that the method of treatment continue "for a period of at least 12 weeks."

438. This limitation is similar to a limitation in Claim 1 of the '728 Patent, which requires that the method of treatment continue "for a period of 12 weeks."

[9] The addition of the article "a" in Claim 13 of the '715 Patent does not change the meaning of this limitation. As a result, the "who does not receive a concurrent lipid altering therapy" limitation of Claim 13 of the '715 Patent and the "who does not receive concurrent lipid altering therapy" limitation of Claim 1 of the '728 Patent are effectively identical.

439. For the reasons discussed at ¶¶ 354–83 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products for 12 weeks and frequently longer. Accordingly, Defendants will induce infringement of the "for a period of 12 weeks" limitation in Claim 1 of the '728 Patent.

440. If Defendants' proposed labeling encourages, promotes, recommends, or suggests administration of Defendants' Products "for a period of 12 weeks," it necessarily encourages, promotes, recommends, or suggests administration "for a period of at least 12 weeks." Moreover, no party has argued that the minor difference between "for a period of 12 weeks" and "for a period of 12 weeks" affects the infringement analysis in any way.

441. Accordingly, Defendants will induce infringement of the "for a period of at least 12 weeks" limitation that Claim 14 of the '715 Patent incorporates by way of its dependence from Claim 13.

442. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"for a period of at least 12 weeks" as required by Claim 14 of the '715 Patent.

2. "to effect a statistically significant reduction in triglycerides"

443. Defendants' will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products "to effect a statistically significant reduction in triglycerides." The same section further conveys to physicians that such a reduction will in fact occur in their patients.

444. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA®'s labeling, reports that 4 g per day of icosapent ethyl effected a 33% reduction in TG compared to placebo in patients with severe hypertriglyceridemia. Notably, Table 2 specifically states that the 33% reduction in TG was statistically significant by reporting a p-value of less than 0.001. PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000012,

DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

445. Clinicians will read this section of Defendants' labeling as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of icosapent ethyl, with the intent and expectation that those results will in fact be achieved. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.".

446. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction in triglycerides" as required by Claim 14 of the '715 Patent.

3. "to effect a statistically significant reduction . . . in apolipoprotein B"

447. Defendants' will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products "to effect a statistically significant reduction . . . in apolipoprotein B." The same section further conveys to physicians that such a reduction will in fact occur in their patients.

448. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA®'s labeling, reports that 4 g per day of icosapent ethyl effected a 9% reduction in apoB compared to placebo. Table 2 further states that the 9% reduction in apoB was statistically significant by reporting a p-value of less than 0.05. PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

449. By instructing clinicians that 4 g per day of icosapent ethyl has been shown to cause a statistically significant reduction in TGs *and* apoB when administered to adult patients with severe hypertriglyceridemia, the Clinical Studies section of Defendants' labeling encourages, recommends, promotes, or suggests that clinicians administer Defendants' ANDA Products with the intent to effect a statistically significant reduction in TGs while having the additional beneficial effect of a statistically significant reduction in apoB. Table 2 further confirms that physicians will observe such a reduction in their patients. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

450. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction . . . in apolipoprotein B" as required by Claim 14 of the '715 Patent.

4. "without effecting a statistically significant increase of LDL-C"

451. The court previously construed the term "without effecting a statistically significant increase in LDL-C" to mean "without bringing about a rise in LDL-C attributable to the treatment rather than to chance." Claim Construction Order, at 9–10 (ECF No. 135).

452. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to effect a reduction of TGs in a severely hypertriglyceridemic patient without effecting a statistically significant increase in LDL-C—an increase in LDL-C that is attributable to the TG-lowering treatment rather than to chance.

453. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA®'s labeling, reports that patients treated with 4 g per day of icosapent ethyl experienced a 2% reduction in LDL-C

compared to placebo. The Clinical Studies section further states that "[t]he reduction in [triglycerides] observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

454. This LDL-C decrease is not reported as being a statistically significant decrease, but there was also no statistically significant increase. Thus, there was no statistically significant change in LDL-C up or down. That said, the data demonstrates a trend toward decreasing LDL-C.

455. By communicating to clinicians that icosapent ethyl reduced LDL-C, Defendants' labels necessarily encourage, recommend, promote, or suggest to clinicians that Defendants' ANDA Products will not raise LDL-C, let alone raise LDL-C by an amount that would lead one to believe that the rise was attributable to the treatment rather than to chance. There can be no "rise in LDL-C attributable to the treatment rather than to chance" because there was no rise in LDL-C. Therefore, clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

456. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"without effecting a statistically significant reduction in LDL-C" as required by Claim 14 of the '715 Patent.

* * *

457. Clinicians will perform each of the method steps in Claim 14 of the '715 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XV. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 1 OF THE '677 PATENT.

A. Claim 1 of the '677 Patent

458. Claim 1 of the '677 Patent is an independent claim.

459. Claim 1 of the '677 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.

PX 25 at 000021, U.S. Patent No. 8,357,677 at AMRN-PEXP-0000066.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 1 of the '677 Patent

460. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the limitations in Claim 1 of the '677 Patent that describe the pharmaceutical product that is to be used in this method claim.

461. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

462. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters." Joint Stipulated Facts, ¶¶ 205, 217, 229 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 1

463. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 1 of the '677 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "administering orally to the subject about 4 g per day of a pharmaceutical composition"
- "for a period of at least about 12 weeks"
- "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control"

See PX 25 at 000021, U.S. Patent No. 8,357,677 at AMRN-PEXP-0000066.

464. As discussed above, Defendants will induce infringement of the following disputed limitations in Claims 1 of the '677 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," *see supra* ¶¶ 308–20;
- "administering orally to the subject about 4 g per day of a pharmaceutical composition," *see supra* ¶¶ 333–53; and
- "for a period of at least about 12 weeks," *see supra* ¶¶ 354–83.[10]

465. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' labeling, if approved, will directly infringe the remaining limitations in Claim 1 of the '677 Patent:

- "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control"

[10] This limitation differs slightly from the language of Claim 1 of the '728 Patent and Claim 14 of the '715 Patent in that it recites a treatment duration of "at least *about* 12 weeks." However, if Defendants' proposed labeling encourages, promotes, recommends, or suggests administration of Defendants' Products "for a period of 12 weeks," it necessarily encourages, recommends, and promotes administration "for a period of at least about 12 weeks." Moreover, no party has argued that the minor difference between "for a period of 12 weeks," "for a period of at least 12 weeks," or "for a period of at least about 12 weeks" affects the infringement analysis in any way.

466. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 1 of the '677 Patent for the reasons described below.

1. "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control"

467. This limitation is similar to the limitation in Claim 1 of the '728 Patent that requires administration of the pharmaceutical composition "to effect a reduction in triglycerides without substantially increasing LDL-C." The only difference is that, in Claim 1 of the '728 Patent, the comparison is "to a second subject" who had not received the therapy, whereas in Claim 1 of the '677 Patent the comparison is "to placebo control."

468. Under the Court's construction of the "compared to" limitations, that difference does not impact the meaning of the claims. As discussed above, under the Court's construction of "compared to," this claim term simply refers to "a comparison between what happens when the treatment is administered versus what would otherwise happen to a second subject" who does not receive treatment. Claim Construction Order, at 12–13 (ECF No. 135). In other words, the "compared to" term merely "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects." *See also supra* ¶¶ 401–02.

469. As discussed above, the placebo group in the clinical study reported in the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, represents a group of subjects who received a placebo rather than the studied treatment (4 g per day of icosapent ethyl). *See supra* ¶ 404.

470. Accordingly, under the Court's construction of the "compared to" terms in the Asserted Claims, the limitations requiring administration of the pharmaceutical composition to effect a reduction in triglycerides without substantially increasing LDL-C "compared to a second subject" who does not receive the composition (as required by Claim 1 of the '728 Patent) and administration of the composition to cause the same effects "compared to placebo control" (as required by Claim 1 of the '677 Patent) are effectively identical.

471. Accordingly, for the reasons discussed at ¶¶ 384–400 above, and the reasons reiterated below, Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control."

472. ***Clinical Studies Section.*** As noted previously, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA®'s labeling, reports the results of a placebo-controlled study in which investigators administered 4 g per day of icosapent ethyl to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Table 2 in the Clinical Studies section reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received icosapent ethyl, compared to baseline and compared to placebo. This information provides a comparison of the lipid effects experienced by the group who received icosapent ethyl to the lipid effects observed in patients who received only a placebo. PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; *see also* PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

473. The label instructs clinicians on the degree to which icosapent ethyl beneficially alters lipid levels in patients with severe hypertriglyceridemia from their pre=treatment levels. Defendants' labeling thereby encourages clinicians to administer Defendants' ANDA Products to administer Defendants' ANDA Products to severely hypertriglyceridemic patients with the intent and expectation that these beneficial lipid effects will in fact be achieved.

474. As relevant to this limitation, Table 2 instructs clinicians that patients who were administered icosapent ethyl experienced a median 27% reduction in TG levels from baseline and a median 5% reduction in LDL-C levels from baseline, while patients in the placebo group experienced a median 10% increase in TG levels from baseline and a median 3% reduction in

LDL-C compared to baseline. Critically, Table 2 further instructs clinicians that the administration of icosapent ethyl 4 g per day for 12 weeks caused a median 33% reduction in TGs and a median 2% reduction in LDL-C when compared to placebo control (*i.e.*, compared to the 75 patients who did not receive the treatment). Furthermore, the TG reduction from baseline relative to placebo was statistically significant. While the LDL-C reduction compared to placebo was not statistically significant, median LDL-C levels also did not increase, let alone increase substantially. *See supra* ¶¶ 390, 396.

475. The Clinical Studies section of Defendants' labeling (and VASCEPA®'s labeling) thus instructs clinicians that icosapent ethyl 4 g per day reduces TGs without substantially raising LDL-C compared to placebo control when administered for 12 weeks. Clinicians will read the Defendants' labeling as encouraging, recommending, promoting, or suggesting that clinicians administer Defendants' ANDA Products with the intent and expectation that they will reduce TGs in their severely hypertriglyceridemic patients while having the additional beneficial effect of not substantially raising those patients' LDL-C levels (compared to what they would have been with no treatment). Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

476. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control" as required by Claim 1 of the '677 Patent.

* * *

477. Clinicians will perform each of the method steps in Claim 1 of the '677 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XVI. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 8 OF THE '677 PATENT

A. Claim 8 of the '677 Patent

478. Claim 8 of the '677 Patent is a dependent claim that depends from Claim 1 of the '677 Patent.

479. As a dependent claim, Claim 8 incorporates the limitations in Claim 1.

480. Claim 1 of the '677 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.

PX 25 at 000021, U.S. Patent No. 8,357,677 at AMRN-PEXP-0000066.

481. Claim 8 of the '677 Patent recites:

> The method of claim 1, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of at least about 12 weeks to effect a reduction in apolipoprotein B compared to placebo control.

PX 25 at 000022, U.S. Patent No. 8,357,677 at AMRN-PEXP-0000067.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 8 of the '677 Patent

482. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 8 of the ''677 Patent that describe the pharmaceutical product that is to be used in this method claim.

483. First, Defendants have stipulated that their products, as well as VASCEPA® contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324)

484. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96%, by weight of all

fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters." Joint Stipulated Facts, ¶¶ 205, 217, 229 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 8

485. As a dependent claim, Claim 8 of the '677 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '677 Patent.

486. For the reasons discussed at Paragraphs 467–77 above, Defendants will induce infringement of all limitations in Claim 1 of the '677 Patent.

487. Defendants dispute whether they will induce clinicians to infringe the remaining limitations in Claim 8 of the '677 Patent:

- "administering to the subject about 4 g of the pharmaceutical composition daily"
- "for the period of at least about 12 weeks"
- "to effect a reduction in apolipoprotein B compared to placebo control"

See PX 25 at 000022, U.S. Patent No. 8,357,677 at AMRN-PEXP-0000067.

488. As discussed above, Defendants will induce infringement of the following disputed limitations in Claim 8 of the '677 Patent:

- "administering to the subject about 4 g of the pharmaceutical composition daily," *see supra* ¶¶ 333–53, 463–77; and
- "for the period of at least about 12 weeks," *see supra* ¶¶ 354–83, 437–42, 467–77.

489. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitation in Claim 8 of the '677 Patent:

- "to effect a reduction in apolipoprotein B compared to placebo control"

490. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitation in Claim 8 of the '677 Patent for the reasons described below.

1. "to effect a reduction in apolipoprotein B compared to placebo control"

491. As discussed above, per the Court's construction of "compared to," this claim term refers to "a comparison between what happens when the treatment is administered versus what would otherwise happen to a second subject" who is not administered the treatment. Claim Construction Order, at 12–13 (ECF No. 135). The "compared to" term merely "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects." *Id.*; *see also supra* ¶¶ 401–02.

492. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia "to effect a reduction in apolipoprotein B compared to placebo control."

493. ***Clinical Studies Section.*** As noted previously, the Clinical Studies section in Defendants' labeling, like the Clinical Studies section in VASCEPA®'s labeling, reports the results of a placebo-controlled study in which investigators administered 4 g per day of icosapent ethyl to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Table 2 in the Clinical Studies section reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received icosapent ethyl, compared to baseline and compared to placebo. This information provides a comparison of the lipid effects experienced by the group who received icosapent ethyl to the lipid effects observed in patients who received only a placebo. *See* PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

494. By teaching clinicians the degree to which icosapent ethyl can beneficially alter lipid levels in patients with severe hypertriglyceridemia compared to what happens in patients

who do not receive the drug, Defendants' labeling encourages clinicians to administer Defendants' ANDA Products to severely hypertriglyceridemic patients with the intent to cause these beneficial lipid effects.

495. As relevant to this limitation, Table 2 instructs clinicians that patients who were administered icosapent ethyl experienced a median 4% reduction in apoB levels from baseline, while patients in the placebo group experienced a median 4% increase in apoB levels from baseline. Critically, Table 2 further instructs clinicians that administration of icosapent ethyl 4 g per day for 12 weeks caused a median 9% reduction in apoB when compared to placebo control (*i.e.*, compared to the 75 patients who did not receive the treatment). Furthermore, the apoB reduction from baseline relative to placebo was statistically significant.

Table 2: Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	Icosapent Ethyl 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33[1] (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29[2] (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9[2] (-14, -3)

% Change = Median Percent Change from Baseline
Difference = Median of [Icosapent Ethyl % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test
1. p-value < 0.001 (primary efficacy endpoint)
2. p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; *see also* PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

496. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that icosapent ethyl 4 g per day reduced both TGs and apoB from baseline relative to placebo in severely hypertriglyceridemic patients.

Icosapent ethyl 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo.

PX 274 at 000007, Hikma Prescribing Information (2016) at WWIC0-NV-002841; *see also* PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

497. The Clinical Studies section of Defendants' labeling (and VASCEPA®'s labeling) thus instructs clinicians that icosapent ethyl 4 g per day reduces apoB compared to placebo control when administered for at least 12 weeks. Clinicians will read this section of Defendants' labeling as encouraging, recommending, promoting, or suggesting that they administer 4 g per day of icosapent ethyl, with the intent and expectation that their severely hypertriglyceridemic patients will experience a reduction in TGs while having the additional beneficial effect of reducing those patients' apoB levels (compared to what they would have been with no treatment). Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

498. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in apolipoprotein B compared to placebo control," as required by Claim 8 of the '677 Patent.

* * *

499. Clinicians will perform each of the method steps in Claim 8 of the '677 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XVII. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 1 OF THE '652 PATENT

A. Claim 1 of the '652 Patent

500. Claim 1 of the '652 Patent is an independent claim.

501. Claim 1 of the '652 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of

> a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.

PX 26 at 000022, U.S. Patent No. 8,367,652 at AMRN-PEXP-0000089.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 1 of the '652 Patent

502. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 1 of the '652 Patent that describe the pharmaceutical product that is to be used in this method claim.

503. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

504. Second, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA®, comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters." Joint Stipulated Facts, ¶¶ 205, 217, 229 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 1

505. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 1 of the '652 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "administering orally to the subject about 4 g per day of a pharmaceutical composition"
- "for a period of about 12 weeks"
- "to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline"

See PX 26 at 000022, U.S. Patent No. 8,367,652 at AMRN-PEXP-0000089.

506. As discussed above, Defendants will induce infringement of the following disputed limitations in Claim 1 of the '652 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," *see supra* ¶¶ 308–20; and
- "administering orally to the subject about 4 g per day of a pharmaceutical composition," *see supra* ¶¶ 333–353.

507. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claim 1 of the '652 Patent:

- "for a period of about 12 weeks"
- "to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline"

508. Furthermore, Defendants' proposed labeling will induce clinicians to infringe the remaining limitations in Claim 1 of the '652 Patent for the reasons described below.

1. "for a period of about 12 weeks"

509. Claim 1 of the '652 Patent requires that the method of treatment continue "for a period of about 12 weeks." The parties have agreed that the term "about" as used in the Asserted Claims means "approximately." Agreed Constructions of the Claim Terms at 4 (ECF No. 83–2).

510. This limitation is similar to a limitation in Claim 1 of the '728 Patent, which requires that the method of treatment continue "for a period of 12 weeks."

511. For the reasons discussed at ¶¶ 354–383, 437–42, and 467–77 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products for 12 weeks and frequently longer. Accordingly, Defendants will induce infringement of the "for a period of 12 weeks" limitation in Claim 1 of the '728 Patent.

512. If Defendants' proposed labeling encourages, recommends, promotes, or suggests administration of Defendants' ANDA Products "for a period of 12 weeks," it necessarily

encourages, recommends, and promotes administration "for a period of about 12 weeks." Moreover, no party has argued that the minor difference between "for a period of 12 weeks" and "for a period of about 12 weeks" affects the infringement analysis in any way.

513. Accordingly, Defendants will induce infringement of the "for a period of about 12 weeks" limitation in Claim 1 of the '652 Patent.

514. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"for a period of about 12 weeks," as required by Claim 1 of the '652 Patent.

2. "to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline"

515. Claim 1 of the '652 Patent requires that the pharmaceutical composition be administered "to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline."

516. This limitation is similar to the limitations in Claim 1 of the '728 Patent and Claim 1 of the '677 Patent that require administration of the pharmaceutical composition "to effect a reduction in triglycerides without substantially increasing LDL-C." The only difference is that in Claim 1 of the '652 Patent the effect is measured "compared to baseline," rather than as "compared to a second subject" (as in Claim 1 of the '728 Patent) or as "compared to placebo" (as in Claim 1 of the '677 Patent). *See supra* ¶¶ 401–02, 468.

517. Under the Court's construction, the claim term "compared to" as used in the Asserted Claims simply refers to "a comparison between what happens when treatment is administered versus what would otherwise happen." Claim Construction Order, at 12–13 (ECF No. 135). In essence, the "compared to" term merely "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects." *See also supra* ¶¶ 401–02.

518. In Claim 1 of the '652 Patent, the comparison is to baseline. Baseline, as used in this claim limitation, refers to a patient's lipid levels prior to initiating treatment. As a result, this limitation requires administration of the pharmaceutical composition to reduce a patient's TG

levels (without substantially increasing the patient's LDL-C levels) from their pre-treatment levels.

519. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia "to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline."

520. ***Clinical Studies Section.*** As noted previously, the Clinical Studies section of Defendants' labeling, like the same section of the VASCEPA® labeling, reports the results of a placebo-controlled study in which investigators administered 4 g per day of icosapent ethyl to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Table 2 in the Clinical Studies section reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received icosapent ethyl, compared to baseline and compared to placebo. *See* PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095601–02; PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

521. The label instructs clinicians on the degree to which icosapent ethyl beneficially alters lipid levels in patients with severe hypertriglyceridemia from their pre-treatment levels. Defendants' labeling thereby encourages clinicians to administer Defendants' ANDA Products to severely hypertriglyceridemic patients with the intent to cause these beneficial lipid effects. Furthermore the Clinical Studies section demonstrates that clinicians will in fact observe such results in their patients.

522. As relevant to this limitation, Table 2 instructs clinicians that administration of icosapent ethyl 4 g per day for 12 weeks caused patients a median 27% reduction in TG levels from baseline and a median 5% reduction in LDL-C levels from baseline.

Table 2: Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	Icosapent Ethyl 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33[1] (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29[2] (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9[2] (-14, -3)

% Change = Median Percent Change from Baseline
Difference = Median of [Icosapent Ethyl % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test
1. p-value < 0.001 (primary efficacy endpoint)
2. p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; *see also* PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

523. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that icosapent ethyl 4 g per day reduced TGs without raising LDL-C.

> Icosapent ethyl 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo.

PX 274 at 000007, Hikma Prescribing Information (2016) at WWIC0-NV-002841; *see also* PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

524. Clinicians will therefore read Defendants' labeling (VASCEPA®'s labeling) and as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of icosapent ethyl, with then intent and expectation that they will reduce their severely hypertriglyceridemic patients' TGs from baseline, without substantially increasing patients' LDL-C levels. Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

525. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline," as required by Claim 1 of the '652 Patent.

* * *

526. Clinicians will perform each of the method steps in Claim 1 of the '652 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XVIII. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 4 OF THE '560 PATENT.

A. Claim 4 of the '560 Patent

527. Claim 4 of the '560 Patent is a dependent claim that depends from Claim 1 of the '560 Patent.

528. As a dependent claim, Claim 4 incorporates the limitations in Claim 1.

529. Claim 1 of the '560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject.

PX 30 at 000022, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000182.

530. Claim 4 of the '560 Patent recites:

> The method of claim 1, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject.

PX 30 at 000023, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000183.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 4 of the '560 Patent

531. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 4 of the '560 Patent that describe the pharmaceutical product that is to be used in this method claim.

532. First, the Hikma Defendants stipulated that their ANDA Product comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 220.

533. Second, the DRL Defendants stipulated that their ANDA Product comprises a "capsule comprising . . . not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 233.

534. Third, the DRL Defendants stipulated that their ANDA Product comprises a "capsule comprising 950 mg to 1050 mg of ethyl eicosapentaenoate." Joint Stipulated Facts ¶ 232.

535. Fourth, the DRL Defendants further stipulated that they will not assert the limitation requiring a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate" as a basis for noninfringement of Claim 4 of the '560 Patent. Joint Stipulated Facts ¶ 232.[11]

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 4

536. As a dependent claim, Claim 4 of the '560 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '560 Patent.

[11] Similarly, Defendants stipulated that VASCEPA® comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 208.

537. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 4 of the '560 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "administering orally to the subject 4 capsules per day"
- "for a period of 12 weeks"
- "effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject"

PX 30 at 000022–23, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000182–83.

538. As discussed above, Defendants will induce infringement of the following disputed limitations in Claim 4 of the '560 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," *see supra* ¶¶ 308–20; and
- "for a period of 12 weeks," *see supra* ¶¶ 354–83, 437–42, 467–77.

539. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claim 4 of the '560 Patent:

- "administering orally to the subject 4 capsules per day"
- "effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject"

540. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 4 of the '560 Patent for the reasons described below.

1. "administering orally to the subject 4 capsules per day"

541. Defendants will induce infringement of this limitation because clinicians will read the Dosage and Administration and Patient Counseling Information sections of Defendants' labeling as encouraging, recommending, promoting, or suggesting the oral administration of "4

capsules per day," and Defendants' proposed Patient Information will further encourage patients to orally ingest 4 capsules per day.

542. For the reasons discussed at ¶¶ 333–43 above, Defendants will induce infringement of the requirement in Claim 4 of the '560 Patent that the capsules be "administered orally."

543. Additionally, for the reasons discussed at ¶¶ 344 –53 above, Defendants' proposed labeling will induce clinicians to administer 4 grams per day taken as 2 1-gram capsules twice daily with food, and patients will take the medication as directed, as stated in Claim 4 of the '560 Patent. Indeed, in the Parties' Joint Stipulated Facts, Defendants stipulated that the dosage form of their ANDA Products is a 1-gram soft-gelatin capsule. Joint Stipulated Facts ¶¶ 225, 213; *see also id.* ¶ 201 (VASCEPA®).

544. ***Dosage and Administration Section.*** The Dosage and Administration section of Defendants' labeling, like the same section of VASCEPA®'s labeling, instructs clinicians that the daily dose of Defendants' ANDA Products is 4 grams per day taken as two (1-gram) capsules twice daily with food. PX 274 at 000002, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002836; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169. Defendants' proposed labeling thus encourages or instructs doctors to prescribe 4 capsules per day of Defendants' ANDA products.

545. ***Patient Counseling Information.*** The Patient Counseling Information section of Defendants' labeling, like the same section in VASCEPA®'s labeling, recommends that clinicians "[i]nstruct patients to take icosapent ethyl as prescribed"—*i.e.*, as 4 capsules per day, delivered in a twice daily dose of 2 capsules. PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000013, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095603; *see also* PX 940 at 000008, VASCEPA® Prescribing Information (2017) at AMRN03132175.

546. ***Patient Information.*** Defendants' labeling further encourages patients to abide by their clinician's instructions and take the prescribed 4 capsules per day. The Patient Information that, if approved, would accompany Defendants' labeling advises patients to "[t]ake icosapent ethyl exactly as your doctor tells you to take it" and to "not change your dose . . .without talking to your doctor." The Patient Information also specifically instructs patients to take 4 capsules per day (and no more). PX 274 at 0000008, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002842; PX 574 at 0000015, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095605; PX 940 at 000009, VASCEPA® Prescribing Information (2017) at AMRN03132176.

547. Defendants' proposed labeling thus encourages, recommends, and promotes physicians to prescribe, and patients to orally ingest, 4 capsules per day. Defendants' proposed labeling will thus induce clinicians to infringe this limitation of Claim 4 of the '560 Patent.

548. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—by "administering orally to the subject 4 capsules per day," as required by Claim 4 of the '560 Patent.

2. "effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject"

549. Claim 4 adds to Claim 1 the additional limitation: "wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject."

550. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to "effect[] a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject." This section further conveys to physicians that such effects will in fact occur in patients.

551. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' proposed labeling, like the same table in VASCEPA®'s labeling, reports that, when administered for 12 weeks to patients with severe hypertriglyceridemia, icosapent ethyl 4 g per day caused a median 27% in triglycerides from baseline and a median 33% reduction in triglycerides compared to placebo. PX 274 at 000006, Hikma Proposed Prescribing Information at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

552. Table 2 in the Clinical Studies section further instructs clinicians that patients treated with 4 g per day of icosapent ethyl experienced a median 5% reduction in LDL-C compared to baseline, as well as a median 2% reduction in LDL-C compared to placebo. PX 274 at 000006, Hikma Proposed Prescribing Information at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

553. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that icosapent ethyl 4 g per day "reduced median TG . . . levels from baseline relative to placebo" and that "[t]he reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 274 at 000007, Hikma Proposed Prescribing Information at WWIC0-NV-002841; PX 574 at 000012, DRL Proposed Prescribing Information at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

554. As explained above, a clinician reading Defendants' labeling (or VASCEPA®'s labeling) would understand that these lipid measurements were taken in a fasting state. *See supra* ¶¶ 314–20.

555. In sum, the Clinical Studies section of Defendants' labeling (and the VASCEPA® labeling) instructs clinicians that patients who were administered 4 g per day of icosapent ethyl for 12 weeks experienced reductions in TGs in excess of the minimum "at least 10%" reduction

required by Claim 4 of the '560 Patent, and did not experience an increase of LDL-C of more than 5% (but instead saw an reduction in LDL-C compared to baseline and placebo).

556. Clinicians will read this section of Defendants' labeling (and VASCEPA®'s labeling) as encouraging, recommending, promoting, or suggesting that they administer 4 g per day of icosapent ethyl, with the intent and expectation that Defendants' ANDA Products will reduce severely hypertriglyceridemic patients' TGs by more than "at least 10%" without increasing patients' LDL-C levels by "more than 5%." Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

557. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—to "effect[] a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject" as required by Claim 4 of the '560 Patent.

* * *

558. Clinicians will perform each of the method steps in Claim 4 of the '560 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XIX. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 17 OF THE '560 PATENT.

A. Claim 17 of the '560 Patent

559. Claim 17 of the '560 Patent is a dependent claim that depends from Claim 11 of the '560 Patent.

560. As a dependent claim, Claim 17 incorporates the limitations in Claim 11.

561. Claim 11 of the '560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic

> acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject compared to placebo control.

PX 30 at 000023, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000183.

562. Claim 17 of the '560 Patent recites:

> The method of claim 11, wherein said administering effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control.

PX 30 at 000023, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000183.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 17 of the '560 Patent

563. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 17 of the '560 Patent that describe the pharmaceutical product that is to be used in this method claim.

564. First, the Hikma Defendants stipulated that their ANDA Product comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 220.

565. Second, the DRL Defendants stipulated that their ANDA Product comprises a "capsule comprising . . . not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 233.

566. Third, the DRL Defendants stipulated that their ANDA Product comprises a "capsule comprising 950 mg to 1050 mg of ethyl eicosapentaenoate." Joint Stipulated Facts ¶ 232.

567. Fourth, the DRL Defendants further stipulated that they will not assert the limitation requiring a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate" as a basis for noninfringement of Claim 17 of the '560 Patent. Joint Stipulated Facts ¶ 232.[12]

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 17

568. As a dependent claim, Claim 17 of the '560 Patent incorporates the limitations of the claim from which it depends, Claim 11 of the '560 Patent.

569. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 17 of the '560 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "administering orally to the subject 4 capsules per day"
- "for a period of 12 weeks"
- "effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control"

See PX 30 at 000023, U.S. Patent No. 8,431,560 at AMRN-PEXP-0000183.

570. As discussed above, Defendants will induce infringement of the following disputed limitations in Claims 17 of the '560 Patent:

- "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl," *see supra* ¶¶ 308–20;
- "administering orally to the subject 4 capsules per day," *see supra* ¶¶ 541–48; and
- "for a period of 12 weeks," *see supra* ¶¶ 354–83, 437–42, 467–77.

[12] Similarly, Defendants stipulated that VASCEPA® comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present." Joint Stipulated Facts ¶ 208.

571. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the only remaining limitation of Claim 17 of the '560 Patent:

- "effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control"

572. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitation in Claim 17 of the '560 Patent for the reasons described below.

1. "effects reduction in fasting triglycerides of at least 20% without increasing LDL-C in the subject compared to placebo control"

573. For the reasons discussed at ¶¶ 467–77 above, Defendants' proposed labeling will encourage, recommend, promote, and suggest that clinicians administer Defendants' ANDA Products "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control," as required by Claim 1 of the '677 Patent, and conveys that such effects will in fact occur in patients with severe hypertriglyceridemia.

574. This limitation differs from that limitation in Claim 1 of the '677 Patent only in the magnitude of the lipid effects disclosed. Whereas Claim 1 of the '677 Patent required a reduction in TGs, this limitation requires a reduction in TGs of at least 20%. And whereas Claim 1 of the '677 Patent required the reduction in TGs without *substantially increasing* LDL-C, this limitation requires that TGs be reduced (by at least 20%) without *increasing* LDL-C.

575. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labels, like the Clinical Studies section of the VASCEPA® label, as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA Products to "effect[] a reduction in fasting triglycerides of at least 20% without increasing LDL-C in the subject compared to placebo control." The Clinical Studies section further conveys to physicians that such effects will in fact occur in their patients.

576. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in VASCEPA®'s labeling, instructs clinicians that 4 g per day of

icosapent ethyl, when administered to severely hypertriglyceridemic patients for 12 weeks, effected a median 33% reduction in TGs compared to placebo and a median 2% reduction in LDL-C compared to placebo. PX 274 at 000006, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

577. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that "[i]cosapent ethyl 4 grams per day reduced median TG . . . levels from baseline relative to placebo," and that "[t]he reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

578. As explained above, a clinician reading Defendants' labeling (or VASCEPA®'s labeling) would understand that these lipid measurements were taken in a fasting state. *See supra* ¶¶ 314–20.

579. The Clinical Studies section of Defendants' labeling thus instructs clinicians administering 4 g per day of icosapent ethyl for at least 12 weeks, they can expect to reduce many patients' fasting TG levels by more than "at least 20%" without increasing LDL-C compared to placebo, as required by Claim 17 of the '560 Patent.

580. Clinicians will read this section of Defendants' labeling (and VASCEPA®'s labeling) as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of icosapent ethyl, with the intent and expectation that Defendants' ANDA Products will reduce severely hypertriglyceridemic patients' fasting TG levels by at least 20% without increasing LDL-C compared to placebo. Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the

claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling..

581. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—to "effect[]reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control," as required by Claim 17 of the '560 Patent.

* * *

582. Clinicians will perform each of the method steps in Claim 17 of the '560 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XX. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 1 OF THE '929 PATENT

A. Claim 1 of the '929 Patent

583. Claim 1 of the '929 Patent is an independent claim.

584. Claim 1 of the '929 Patent recites:

> A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

PX 31 at 000022–000023, U.S. Patent No. 8,518,929 at AMRN-PEXP-0000205–06.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 1 of the '929 Patent

585. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 1 of the '929 Patent that describe the pharmaceutical product that is to be used in this method claim.

586. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

587. Second, Defendants have stipulated that the "pharmaceutical composition" in a daily dose of Defendants' ANDA Products, as well as in a daily dose of VASCEPA®, comprises "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or it esters, by weight of all fatty acids." Joint Stipulated Facts, ¶¶ 209, 221, 234 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 1

588. Defendants dispute whether they will induce clinicians to infringe the following limitations in Claim 1 of the '929 Patent:

- "A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl"
- "orally administering to the subject daily . . . a pharmaceutical composition"
- "for at least about 12 weeks"

See PX 31 at 000022–000023, U.S. Patent No. 8,518,929 at AMRN-PEXP-0000205–06.

589. As discussed above, Defendants will induce direct infringement of the following disputed limitations in Claims 1 of the '929 Patent:

- "orally administering to the subject daily . . . a pharmaceutical composition," *see supra* ¶¶ 333–53;[13] and
- "for at least about 12 weeks," *see supra* ¶¶ 354–83, 437–42, 467–77.[14]

[13] Claim 1 of the '929 Patent uses the language "orally administering to the subject *daily*" whereas other claims, such as Claim 1 of the '728 Patent use the language "per day." The parties have not asserted that there is any meaningful distinction in this slight difference. It does not change the analysis for this limitation in any way.

[14] Like the similar limitation in Claim 1 of the '677 Patent ("for a period of at least about 12 weeks"), this limitation differs from the language of Claim 1 of the '728 Patent and Claim 14 of the '715 Patent in that it recites a treatment duration of "at least *about* 12 weeks." However, if Defendants' labeling encourages, promotes, recommends, or suggests administration of Defendants' ANDA Products "for a period of 12 weeks," it necessarily encourages, recommends, and promotes administration "for a period of at least about 12 weeks." Moreover, no party has argued that any difference between "for a period of 12 weeks," "for a period of at least 12 weeks," or "for a period of at least about 12 weeks" affects the infringement analysis in any way.

590. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the only remaining limitation of Claim 1 of the '929 Patent:

- "A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl"

591. Furthermore, Defendants' proposed labels, if approved, will induce clinicians to infringe the remaining limitation in Claim 1 of the '929 Patent for the reasons described below.

1. "A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl"

592. This limitation differs from, for example, the limitation in Claim 1 of the '728 Patent, because it requires that the subject have "fasting triglycerides of at least 500 mg/dl," rather than "a fasting baseline triglyceride level of 500 mg/dl *to about 1500 mg/dl*."

593. The parties agree that the term "at least 500 mg/dl" is construed to mean "500 mg/dl and above." *See* Agreed Constructions of the Claim Terms at 4 (ECF No. 83-2).

594. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage and Clinical Studies sections of Defendants' labels as encouraging, recommending, promoting, or suggesting the use of Defendants' ANDA Products in "[a] method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl."

595. ***Indications and Usage Section.*** As stated in the Indications and Usage section of Defendants' labels, Defendants' "[i]cosapent ethyl capsules," if approved, will be "indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia." PX 274 at 000001, Hikma Proposed Prescribing Information at WWIC0-NV-002835; PX 574 at 00000–6, DRL Proposed Prescribing Information at DRLEEPA 000095596; *see also* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169 ("VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.").

Defendants are thus expressly seeking FDA approval to market their ANDA Products as a method of treatment for reducing triglycerides in (adult) patients with TG ≥ 500 mg/dL.

596. If FDA approves that indication, then Defendants' labeling will instruct clinicians that Defendants' ANDA Products are approved (as safe and effective) to reduce triglycerides in (adult) patients with TG ≥ 500 mg/dL. In so doing, the labeling will encourage, recommend, or promote administration of Defendants' ANDA Products for the indicated use (to reduce TG levels) in the indicated population (adult patients with TG ≥ 500 mg/dL).

597. As explained above, a clinician reading Defendants' labeling (or VASCEPA®'s labeling) would understand that these lipid levels refer to a measurement made in a fasting state. *See supra* ¶¶ 314–20. Defendants' labeling will thus encourage administration of Defendants' ANDA Products to patients with *fasting* baseline TGs ≥ 500 mg/dL.

598. That TG threshold (≥ 500 mg/dL) is the exact TG threshold used to describe the patient population disclosed in Claim 1 of the '929 Patent. Thus, by encouraging administration of Defendants' ANDA Products to reduce TGs in patients with fasting TGs ≥ 500 mg/dL, the Indications and Usage section of Defendants' labeling (like the VASCEPA® labeling) will necessarily encourage use of their products as "[a] method of reducing triglycerides" in patients with "fasting triglycerides of at least 500 mg/dL," as required by Claim 1 of the '929 Patent.

599. ***Clinical Studies Section.*** The Clinical Studies section of Defendants' labeling, like the Clinical Studies section of VASCEPA®'s labeling, further encourages administration of Defendants' ANDA Products to reduce TGs in patients with fasting baseline TG ≥ 500 mg/dL by reporting that icosapent ethyl was effective to reduce TGs in adult patients with "baseline TG levels . . . between 500 and 2,000 mg/dL." Specifically, the Clinical Studies section instructs clinicians that, in this patient population, 4 g per day of icosapent ethyl administered for 12 weeks caused a median 27% reduction in TGs from baseline and a median 33% reduction in TGs compared to placebo. PX 274 at 000006–07, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002840–41; PX 574 at 000011–12, DRL Proposed Prescribing Information (2018)

at DRLEEPA 0095601–02; PX 940 at 000006–07, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

600. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that "[i]cosapent ethyl 4 grams per day reduced median TG . . . levels from baseline relative to placebo" in patients with baseline 500 mg/dL ≤ TG ≤ 2,000 mg/dL. PX 274 at 000007, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002841; PX 574 at 000012, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095602; PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

601. As explained above, a clinician reading Defendants' labeling (or VASCEPA®'s labeling) would again understand that the lipid measurements discussed in the Clinical Studies section were taken in a fasting state. *See supra* ¶¶ 341–20.

602. By instructing clinicians that icosapent ethyl is effective to reduce TGs in patients with *fasting* baseline TG level between 500 and 2,000 mg/dL, the Clinical Studies section of Defendants' labeling (and VASCEPA®'s labeling) encourages administration of Defendants' ANDA Products (or VASCEPA®) to reduce TGs in a wide range of patients that fall within the scope of the patient population disclosed in Claim 1 of the '929 Patent (*i.e.*, patients with TG ≥ 500 mg/dL).

603. As a result, the Clinical Studies section encourages clinicians to administer Defendants' ANDA Products to patients with TG levels within the scope of the patient population disclosed in Claim 1 of the '929 Patent.

604. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—according to "[a] method of reducing triglycerides in a subject having a fasting baseline triglyceride level of at least 500 mg/dl," as required by Claim 1 of the '929 Patent, PX 31 at 000022.

* * *

605. Clinicians will perform each of the method steps in Claim 1 of the '929 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XXI. DEFENDANTS WILL INDUCE INFRINGEMENT OF CLAIM 5 OF THE '929 PATENT

A. Claim 5 of the '929 Patent

606. Claim 5 of the '929 Patent is dependent upon Claim 1 of the '929 Patent.

607. As a dependent claim, Claim 5 incorporates the limitations in Claim 1.

608. Claim 1 of the '929 Patent recites:

> A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

PX 31 at 000022–23, U.S. Patent No. 8,518,929 at AMRN-PEXP-0000205–06.

609. Claim 5 of the '929 Patent recites:

> The method of claim 1, wherein 12 weeks of said daily administration is effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL.

PX 31 at 000023, U.S. Patent No. 8,518,929 at AMRN-PEXP-0000206.

B. Defendants Have Conceded that Their ANDA Products Will Meet Certain Limitations in Claim 5 of the '929 Patent

610. In the Parties' Joint Stipulated Facts, Defendants stipulated that their ANDA Products will meet the following limitations in Claim 5 of the '929 Patent that describe the pharmaceutical product that is to be used in this method claim.

611. First, Defendants have stipulated that their products, as well as VASCEPA®, contain a "pharmaceutical composition." Joint Stipulated Facts, ¶¶ 204, 216, 228 (ECF No. 324).

612. Second, Defendants have stipulated that the "pharmaceutical composition" in a daily dose of Defendants' ANDA Products, as well as in a daily dose of VASCEPA®, comprises

"about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or it esters, by weight of all fatty acids." Joint Stipulated Facts, ¶¶ 209, 221, 234 (ECF No. 324).

C. Defendants' Proposed Labeling Will Induce Clinicians to Use Their ANDA Products in a Manner that Meets the Remaining Limitations in Claim 5

613. As a dependent claim, Claim 5 of the '929 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '929 Patent.

614. For the reasons discussed at Paragraphs 592–605 above, Defendants will induce infringement of all limitations in Claim 1 of the '929 Patent.

615. Defendants dispute whether they will induce clinicians to infringe the remaining limitations in Claim 5 of the '929 Patent:

- "12 weeks of said daily administration"
- "effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL"

See PX 31 at 000023, U.S. Patent No. 8,518,929 at AMRN-PEXP-0000206.

616. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claims 5 of the '929 Patent.

617. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 5 of the '929 Patent for the reasons described below.

1. "12 weeks of said daily administration"

618. This limitation requires the method of treatment continue for "12 weeks."

619. In this way, this limitation is effectively identical to the requirement in Claim 1 of the '728 Patent that the method of treatment continue "for a period of 12 weeks."

620. For the reasons discussed at ¶¶ 588–605 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products for 12 weeks and frequently longer. Accordingly, Defendants will induce infringement of the "for a period of 12 weeks" limitation in Claim 1 of the '728 Patent.

621. If Defendants' proposed labeling encourages, promotes, recommends, or suggests administration of Defendants' Products "for a period of 12 weeks," it necessarily encourages, promotes, recommends, or suggests administration for "12 weeks."

622. Moreover, no party has argued that any difference between the "for a period of 12 weeks" and "wherein 12 weeks" limitations affects the infringement analysis in any way.

623. Accordingly, Defendants will induce infringement of the "wherein 12 weeks" limitation in Claim 5 of the '929 Patent.

624. This limitation further requires "said daily administration." The "said daily administration" refers back to the limitation in Claim 1 of the '929 Patent, from which Claim 5 depends, that the pharmaceutical composition be "orally administering to the subject daily."

625. As explained at ¶ 589 & n.13 above, the limitation "orally administering to the subject daily" in Claim 1 of the '929 Patent is met for the reasons discussed at ¶¶ 333–53 above.

626. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—for "12 weeks of said daily administration," as required by Claim 5 of the '929 Patent.

2. "effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL"

627. For the reasons discussed at ¶¶ 592–605 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to patients "who have fasting triglycerides levels of at least 500 mg/dL."

628. For the reasons discussed at ¶¶ 447–57 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to effect a statistically significant reduction in apoB in patients with fasting baseline TG levels between 500 mg/dL and 1500 mg/dL.

629. For the reasons discussed at ¶¶ 491–99 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to effect a reduction in apoB

compared to placebo control in patients with fasting baseline TG levels between 500 mg/dL and 1500 mg/dL.

630. For these same reasons, and the reasons discussed below, Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies sections of Defendants' labeling as encouraging, recommending, promoting or suggesting administration of Defendants' ANDA products to "effect[]" a "reduc[tion]" in "apolipoprotein B" in patients with fasting baseline TG levels of at least 500 mg/dL."

631. ***Clinical Studies.*** As noted previously, the Clinical Studies section in Defendants' labeling, like the same section in VASCEPA®'s labeling, instructs clinicians that icosapent ethyl was effective to reduce apoB in patients with fasting baseline TG levels between 500 mg/dL and 2,000 mg/dL. Specifically, Table 2 in the Clinical Studies section instructs clinicians that 4 g per day of icosapent ethyl, when administered to such patients for 12 weeks, caused a median 4% reduction in apoB from baseline and a median 9% reduction in apoB compared to placebo. PX 274 at 000006, Hikma Proposed Prescribing Information at WWIC0-NV-002840; PX 574 at 000011–12, DRL Proposed Prescribing Information at DRLEEPA 0095601–02; *see also* PX 940 at 000007–08, VASCEPA® Prescribing Information (2017) at AMRN03132173–74.

632. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that "[i]cosapent ethyl 4 grams per day reduced median . . . Apo B levels from baseline relative to placebo." PX 274 at 000007, Hikma Proposed Prescribing Information at WWIC0-NV-002841; PX 574 at 000012, DRL Proposed Prescribing Information at DRLEEPA 0095602; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174.

633. As explained above, a clinician reading Defendants' labeling (or VASCEPA®'s labeling) would again understand that the baseline TG levels discussed in the Clinical Studies section were taken in a fasting state. *See supra* ¶¶ 314–20.

634. The Clinical Studies section thus instructs clinicians that 4 g per day of icosapent ethyl reduces TGs and apoB in patients with fasting TG levels in excess of 500 mg/dL.

635. Clinicians will read this section of Defendants' labeling (and VASCEPA®'s labeling) as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of icosapent ethyl, with the intent and expectation that Defendants' ANDA Products will reduce severely hypertriglyceridemic patients' TGs while having the additional beneficial effect of reducing the patients' apoB levels. Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

636. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—according to method "effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL," as required by Claim 1 of the '929 Patent.

* * *

637. Clinicians will perform each of the method steps in Claim 5 of the '929 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

XXII. THE ASSERTED CLAIMS DISCLOSE METHODS OF TREATMENT WITHIN THE SCOPE OF THE USE FOR WHICH DEFENDANTS SEEK FDA APPROVAL

638. Claim 1 of the 929 Patent discloses a method of treatment in which a pharmaceutical composition is administered to a patient with fasting baseline TG $\geq$ 500 mg/dL to reduce the patient's TG levels. *See supra* ¶ 584.

639. The remaining Asserted Claims similarly disclose methods of reducing TGs in patients with severe hypertriglyceridemia in which the pharmaceutical composition is effective to reduce a patient's TG levels while also having an additional beneficial effect on the patient's LDL-C and/or apoB levels. *See supra* ¶¶ 301, 415, 428, 459, 481, 501, 530, 562, 609.

640. For the reasons described below, the Asserted Claims disclose methods of using the pharmaceutical composition that are consistent with the indicated use for which Defendants seek FDA approval to market their ANDA Products. As a result, a clinician who administers

Defendants' ANDA Products in a manner that infringes the Asserted Claims would be prescribing Defendants' ANDA Products in an "on-label" manner.

A. The Asserted Claims and Defendants' Proposed Indication Describe Overlapping Patient Populations

641. Claims 1 and 5 of the '929 Patent require administration of the pharmaceutical composition to patients with TG ≥ 500 mg/dL. *See supra* ¶¶ 584, 609.

642. That is the same TG parameter used to identify the approved patient population in Defendants' proposed indication. Defendants seek FDA approval to market their ANDA Products for use in "adult patients with severe (≥500 mg/dL) hypertriglyceridemia." PX 274 at 000001, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 000006, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596.

643. The administration of Defendants' ANDA Products to adult patients with TG ≥ 500 mg/dL would thus be both (1) an on-label use (*i.e.*, a use described in the approved labeling) and (2) a use that meets the patient-population limitations in Claims 1 and 5 of the '929 Patent.

644. The remaining Asserted Claims require administration of the pharmaceutical composition to patients with 500 mg/dL ≤ TG ≤ approximately 1500 mg/dL. *See supra* ¶¶ 301, 415, 428, 459, 481, 501, 530, 562.

645. Patients who have fasting baseline TG levels of 500 mg/dL to about 1500 mg/dL necessarily have TG levels ≥ 500 mg/dL.

646. As a result, the administration of Defendants' ANDA Products to adult patients with TG levels between 500 mg/dL and approximately 1500 mg/dL would again be both (1) an on-label use and (2) a use that meets the patient-population limitations of the remaining claims.

647. Defendants thus seek FDA approval to market their ANDA Products for use in patients (adult patients with TG ≥ 500 mg/dL) that are within the scope of the patient populations disclosed in the Asserted Claims.

B. The administration of Defendants' ANDA Products to reduce TG levels while also reducing apoB and/or without increasing LDL-C is an "on-label" use

648. A clinician who administers Defendants' ANDA Products to reduce TG in adult patient with severe hypertriglyceridemia while also intending to cause the additional beneficial lipid effects disclosed in the Asserted Claims would be using those products in an on-label manner, meaning in a manner consistent with the use described in Defendants' proposed labeling.

649. A clinician who administers Defendants' ANDA Products to reduce TGs in adult patients with severe hypertriglyceridemia would—in addition to infringing the Asserted Claims—be using those products in an on-label manner. That is the exact indication for which Defendants seek FDA approval. *See* PX 274 at 1, Hikma Proposed Prescribing Information (2016) at WWIC0-NV-002835; PX 574 at 6, DRL Proposed Prescribing Information (2018) at DRLEEPA 0095596.

650. A clinician who, when administering Defendants' ANDA Products to reduce TG levels in adult patients with severe hypertriglyceridemia, also intends to and does cause a reduction in apoB, and/or intends to and does avoid an increase in LDL-C, would also be using Defendants' ANDA Products in an on-label manner. In this scenario, the clinician is still administering Defendants' ANDA Products in a manner consistent with the use described in Defendant's proposed labeling. That is, the clinician is still using Defendants' ANDA Products in the approved patient population (adult patients with TG $\geq$ 500 mg/dL) for the indicated use (to reduce TG levels), while also intending to achieve the additional beneficial effects that Defendants labeling shows icosapent ethyl has *when it is administered consistent with its approved indication*.

651. That the Clinical Studies section of Defendants' labeling encourages clinicians to use Defendants' ANDA Products in this manner is consistent with how FDA views the purpose of this section of a drug label. The Clinical Studies section is intended to inform clinical

prescribing decisions by, among other things, showing the drug's treatment effect when it is used consistently with the approved indication. *See supra* ¶¶ 268–79.

652. In short, a clinician who administers a drug to the approved patient population, in the approved dosage, for the purpose for which it is indicated, while hoping to achieve the treatment effect described in the Clinical Studies section, is using the drug in an on-label manner.

* * *

653. For these reasons, a clinician who administers Defendants' ANDA Products in a manner consistent with the Asserted Claims would be using those products in an on-label manner.

XXIII. OBVIOUSNESS LEGAL STANDARD

654. Under 35 U.S.C. § 103, a patent is invalid as obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." Whether a patent claim is obvious is ultimately a question of law based on four underlying factual determinations: (1) "the scope and content of the prior art"; (2) "the level of ordinary skill in the pertinent art"; (3) the "differences between the prior art and the claims at issue"; and (4) "[s]uch secondary considerations as commercial success, long-felt but unsolved needs, [and the] failure of others . . . ." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966).

655. "A party seeking to invalidate a patent based on obviousness must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). Defendants, as the accused infringers, bear the ultimate burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).

656. The determination of obviousness must be done based on the knowledge possessed by one of ordinary skill in the art at the time the invention was made. Thus, it is not permissible to use hindsight after viewing the claimed invention to determine questions of obviousness or to rely at all on the teachings of the claimed invention in determining whether one of ordinary skill in the art would find the invention obvious. *See, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.") (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012)).

657. "Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) (quoting *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

658. An invention is not obvious to try where, even if it would have been obvious to experiment with different options, "'there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Leo Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *Cyclobenzaprine*, 676 F.3d at 1070).

659. Part of the obviousness inquiry will consider whether objective indicia of non-obviousness support the Asserted Claims. "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17–18; *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (explaining that objective evidence of nonobviousness may include copying, long felt but unsolved need, failure

of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans).

660. "Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are 'not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness.'" *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008)). Objective indicia of non-obviousness, "when considered with the balance of the obviousness in the record, guard against hindsight bias." *Cyclobenzaprine*, 676 F.3d at 1079 (citing *Graham*, 383 U.S. at 36).

661. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Indeed, "[i]t is the secondary considerations that are often the most probative and determinative of the ultimate conclusion of obviousness or nonobviousness." *Pro-Mold & Tool Co., Inc. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996).

XXIV. DEFENDANTS CANNOT CARRY THEIR BURDEN OF ESTABLISHING OBVIOUSNESS BY CLEAR AND CONVINCING EVIDENCE

A. Prosecution History

662. As noted above, the Asserted Patents issued from applications that were continuation of the application that issued from the '727 Patent. During the prosecution of the Asserted Patents, Amarin submitted several declarations, from multiple experts including Dr. Harold Bays and Dr. Howard Weintraub, in support of patentability. Amarin also submitted two declarations by Dr. Philip Lavin, a biostatistician. In those declarations, Dr. Lavin evaluated conclusions drawn by the Patent Examiner about three pieces of prior art. Specifically, these declarations addressed the statistical likelihood that subjects with certain baseline triglyceride levels were included in the studies disclosed in the prior art references.

663. When allowing the claims of the '727 Patent, the Patent Examiner included a detailed Statement of Reasons for Allowance in accordance with 37 C.F.R. § 1.104(e) and the specific guidance set forth in section 1302.14 of the Manual of Patent Examination Procedure. PX 63 at 000015, Manual of Patent Examining Procedure (MPEP), Eighth Edition Revisions 8 and 9, excerpt, available at http://www.uspto.gov/web/offices/pac/mpep/, § 1302.14(I) (8th ed., Rev. 7) (July 2008). In granting the '727 Patent, the Examiner relied on objective indicia of non-obviousness—in particular, a showing that the applicants demonstrated unexpected results (an unexpected reduction in apoB), and satisfied a long-felt unmet medical need through their invention of a method of treatment that lowered triglycerides in persons with very high triglycerides without substantially increasing LDL-C, as prior art treatments had done. PX 380 at 000010–13, Notice of Allowability at AMRN03059936–39. The Examiner did not rely on the Lavin Declarations in the Statement of Reasons for Allowance, *see id.* at 000006–11, and the subject of the Lavin Declarations is unrelated to the basis on which the Examiner granted the patents.

664. 37 C.F.R. § 1.104(e) provides that "[i]f the examiner believes that the record of the prosecution as a whole does not make clear his or her reasons for allowing a claim or claims, the examiner may set forth such reasoning." Section 1302.14(I) of the Manual of Patent Examining Procedure ("MPEP") in turn explains that

> where the examiner's actions clearly point out the reasons for rejection and the applicant's reply explicitly presents reasons why claims are patentable over the reference, the reasons for allowance are in all probability evident from the record and no statement should be necessary. Conversely, where the record is not explicit as to reasons, but allowance is in order, then a logical extension of 37 CFR 1.111 and 1.133 would dictate that the examiner should make reasons of record and such reasons should be specific.

PX 63 at 000015, MPEP at 1300-12.; *see also id.* (explaining that the statement of reasons "facilitates evaluation of the scope and strength of a patent by the patentee and the public and may help avoid or simply litigation of a patent").

665. Accordingly, as authorized by 37 C.F.R. § 1.104(e) and consistent with MPEP § 1302.14, the Examiner made the prosecution history record clear by discussing the specific reasons why the claims were patentable in the Reasons for Allowance.

666. Specifically, in the Examiner's Statement of Reasons for Allowance of the claims of the '727 Patent, the Examiner characterized the claims as "a very narrow and specific method," and summarized the claims as follows:

> Patient population: TG levels between 500 mg/dl and 1500 mg/dl (very high) not receiving any lipid altering therapy,
>
> Drug: 96% pure ethyl-EPA with substantially no DHA
>
> Amount: 4 g per day
>
> Dose regimen: at least 12 weeks.

PX 380 at 000008, Notice of Allowability at AMRN03059934.

667. After describing the scope of the claims, the Examiner next acknowledged that the claims were not anticipated because there was no teaching in the prior art administering EPA to the claimed patient population, patients with TGs of 500 mg/dL to about 1500 mg/dL. *See, e.g.*, *id*. at 000009 ("The prior art does not teach the administration of ethyl-EPA to patients having TG levels between 500 and 1500 mg/dl (very high), as such there is no anticipation.").

668. Nevertheless, the Examiner concluded that it would be prima facie obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA. *See, e.g.*, *id.*. When concluding that it was "obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA," the Examiner expressly cited back to "pages 7 and 8 of the non-final rejection dated 03/02/2012." *Id*. Thus, in the Reasons for Allowance the Examiner maintained his view that, even if there was no prior art teaching administration of purified EPA to a patient population of 500 mg/dl or greater, prior art teaching administration of purified EPA to a patient population with "[e]ven a slight overlap in range" established prima facie obviousness. *See id*; *see also* PX 230 at 000008, USPTO Office Action Summary (March 2, 2012) at AMRN03059751.

669. Instead, the Examiner found the pending claims patentable because "Applicant was able to overcome the above 103 obviousness rejection by showing: 1 - Unexpected results, and 2 - Long felt unmet medical need." *See, e.g.*, PX 380 at 000010, Notice of Allowance at AMRN03059936. The Examiner then spent more than three pages specifically discussing the evidence of objective indicia supporting the Examiner's ultimate conclusion that the claims were patentable. *See, e.g.*, *id* at 000010–13.

670. In these pages, the Examiner discussed at length the September 11, 2011 Weintraub and May 16, 2012 Bays declarations and how they evidenced the objective indicia of unexpected results and long-felt unmet medical need that overcame the Examiner's prima facie obviousness rejection. *See, e.g.*, *id.* These are the only declarations discussed in the Examiner's Reasons for Allowance. *See, e.g.*, *id.*

671. However, these are not the only declarations submitted during prosecution of the '727 Patent. Accordingly, the Examiner's Statement of Reasons for Allowance reflects the type of record clarification contemplated by MPEP § 1302.14(II)(A) by inclusion of an examiner's statement of reasons for allowance: when "claims are allowed on the basis of one (or some) of *a number of arguments and/or affidavits* presented, and a statement is necessary to identify which of these arguments and evidence were found to be most persuasive." *See also* PX 63 at 000015, MPEP § 1302.14(III)(A) (providing an exemplary statement involving an affidavit: "[t]he primary reason for allowance of the claims is the inclusion of [a particular range of nickel]. Applicant's second affidavit in example 5 shows unexpected results from this restricted range.").

672. The Examiner's Statement of Reasons for Allowance thus tracks MPEP § 1302.14 by identifying which affidavits of the multiple affidavits that were submitted support the Examiner's allowance of the claims. The Examiner expressly stated that the September 11, 2011 Weintraub and May 16, 2012 Bays declarations provided the basis for overcoming the prima showing of obviousness by establishing both unexpected results and long felt unmet need in the prior art. Any other declarations in the prosecution history were therefore not the basis for the Examiner's reasons for allowance of the claims.

673. The Examiner included a Statement of Reasons for Allowance when allowing the claims of each of the Asserted Patents. Each Statement of Reasons for Allowance contains materially identical reasons for allowing the claims. *See* PX 39 at 006691–6698, File History for US Patent No. 8,293,728 at AMRN00212743–50; PX 40 at 006484–6494, File History for U.S. Patent No. 8,318,715 at AMRN0021925767; PX 41 at 006420–006427, File History for U.S. 8,357,677 at AMRN00225700707; PX 42 at 006359–6367, File History for U.S. Patent 8,367,652 at AMRN00232083–91; PX 50 at 008141–8148, File History for U.S. Patent No. 8,431,560 at AMRN00271214-21; PX 51 at 000547–000554, File History for U.S. Patent No. 8,518,929 at AMRN00287924–31.

B. Prior Art

1. Description of Defendants' primary prior art references

674. In contending that the Asserted Claims would have been obvious, Defendants contend that the Asserted Claims would have been obvious over a combination of:

- Lovaza PDR
- Mori 2000
- Hayashi; and
- Kurabayashi

675. For some claims, Defendants also include WO '900, and for a number of claims, Defendants contend that some of these references are optional.

676. Defendants also propose additional alternative combinations for a subset of the Asserted Claims—in particular, the asserted claims of the '560 and '929 Patents. These combinations include the same references noted above, but also include the Epadel Prescribing Information from 2007 ("Epadel PI 2007").

a) LOVAZA®, Physicians' Desk Reference 2699 (62d ed. 2008) ("LOVAZA® PDR") (PX 1034)

677. In March 2008, LOVAZA® was the only FDA-approved prescription omega-3 fish oil for lowering triglycerides in patients with very high triglycerides, with an indication as

"an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) triglyceride levels." PX 1034 at 000003, LOVAZA® PDR at 2700. LOVAZA® was made from a mix of omega-3 fatty acids, of which the principal components are approximately 465 mg EPA and 375 mg DHA. *See id.* at 000002. This drug had also previously been known and marketed as OMACOR®. Clinical trial results of OMACOR®/LOVAZA® had been reported at least as early as 1997. *See* PX 436, Harris et al., *Safety and efficacy of Omacor in severe hypertriglyceridemia*, 4 J. of Cardiovascular Risk 385 (1997) ("Harris 1997"). A version of LOVAZA® Prescribing Information was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

678. LOVAZA® was associated with a large increase in LDL-C in patients with severely elevated TG levels. As reported in the product's prescribing information, LOVAZA® increased LDL-C in persons with very high triglycerides by almost 50% compared to placebo, which posed (and still poses) concerns about atherosclerosis. PX 1034 at 000003, LOVAZA® PDR at ICOSAPENT_DFNDTS00006712, Table 2. Because LOVAZA® increased LDL-C to such a degree in the very high TG population, the LOVAZA® labeling warned physicians that patients "should be monitored to ensure that the LDL-C level does not increase excessively." *Id.* at 000003 .

679. The LOVAZA® prescribing information did not attribute the rise in LDL-C in patients with very high triglycerides to either DHA or EPA alone, nor would a person of ordinary skill in the art have attributed LOVAZA®'s large LDL-C increase to either EPA or DHA, but to the TG-lowering mechanism of omega-3 fatty acids generally, and to the very-high baseline TG levels of severely hypertriglyceridemic patients, as it was understood that the degree of LDL-C increase was heavily related to the pretreatment triglyceride levels. *See supra* ¶¶ 115–16. Consistent with that understanding, LOVAZA® produced much smaller LDL-C increases in individuals with lower TG levels. *See* PX 939 at 000006, LOVAZA® Statistical Review at AMRN03059165, Table 2 (showing that LOVAZA® increased LDL-C by a median of 4.5% from baseline in patients with high TGs and by 6.9% compared to placebo).

b) Mori et al., *Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids And Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men*, 71 Am. J. Clinical Nutrition 1085 (2000) ("Mori 2000") (DX 1538)

680. Mori 2000 reported the results of a double-blind, placebo-controlled trial of parallel design comparing the effects of 4 g/day EPA versus 4 g/day DHA on 59 overweight mildly hyperlipidemic men. DX 1538 at ICOSAPENT_DFNDTS00011026, Mori 2000 at 1085. Mori 2000's sample size was relatively small, with 19 subjects taking purified EPA, 17 subjects taking DHA, and 20 subjects taking a placebo. *See id*. at ICOSAPENT_DFNDTS00011028, Table 1. Mori 2000 was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

681. Mori 2000 did not study the effects of purified EPA or DHA in persons with triglyceride levels of at least 500 mg/dl, but instead looked at mildly hypercholesterolemic men—with a mean LDL-C level of 166 mg/dl (4.28 mmol/L) and triglyceride level of 178 mg/dl (2.01 mmol/L) for patients administered EPA, and a mean LDL-C level of 165 mg/dl (4.27 mmol/L) and triglyceride level of 199 mg/dl (2.25 mmol/L) for patients administered DHA. *Id*. at ICOSAPENT_DFNDTS00011029, Table 2. Mori 2000 therefore did not teach or create an expectation that high purity EPA would avoid substantial LDL-C increases in persons with very high triglycerides.

682. Mori 2000 reported a variety of lipid effects of EPA, DHA, and placebo. Among the results, Mori 2000 reported for patients administered DHA that the mean LDL-C level increased from 165 mg/dl (4.27 mmol/L) at baseline to 179 mg/dl (4.64 mmol/L) post-intervention, and that for patients administered EPA, the mean LDL-C level increased from 166 mg/dl (4.28 mmol/L) at baseline to 172 mg/dl (4.46 mmol/L) post-intervention. *Id.* Thus, LDL-C increased both for patients administered DHA (by 8%) and EPA (by 3.5%). *Id.* at ICOSAPENT_DFNDTS00011028.

683. A person of ordinary skill in the art reviewing these results would not have been prepared to distinguish the LDL-C effects of EPA and DHA on the basis of these results, even though only DHA's LDL-C increase was statistically significant. This is especially true given the study's small sample size, and that the baseline triglyceride levels of the group taking EPA (2.01 mmol/L or 178 mg/dl) was about 11% lower than the group taking DHA (2.25 mmol/L or 199 mg/dl), since LDL-C increase was understood to be greater as baseline triglyceride levels increased. Nor did prior art reviewing Mori 2000 distinguish DHA and EPA on the basis of their LDL-C effects. *See* PX 905 at 000009, von Schacky, *A review of omega-3 ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels*, 2 Vascular Health and Risk Management 251 (2006) ("von Schacky") at AMRN-PEXP-0007474, Table I (Table showing that DHA and EPA were understood to have the same rising effect on LDL-C).

684. Mori 2000 did not report non-HDL-C data, but non-HDL-C data can be derived by subtracting HDL-C from total cholesterol, both of which Mori 2000 provided. *See* DX 1538 at ICOSAPENT_DFNDTS00011029, Mori 2000 at 1088, Table 2. In patients administered EPA, non-HDL-C decreased by a mere 0.58% compared to baseline—a result that was so slight as to be effectively neutral. That reduction was less than the non-HDL-C reduction of 2.8% calculated for the placebo group. In patients administered DHA, non-HDL-C increased by 1.3% from baseline. Of course, because many of the underlying values that went into these calculations were themselves not statistically significant, a person of ordinary skill in the art would not have understood these results would be statistically significant either.

685. Mori 2000 did not report any apoB data.

686. Mori 2000 taught that DHA has more favorable effects on lipids than EPA, reporting that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations." *Id*. at ICOSAPENT_DFNDTS00011029. Mori 2000 also stated that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable." *Id*. at

ICOSAPENT_DFNDTS00011033. Mori 2000 also noted that "only EPA increased fasting glucose," *id.*, which would have been a concern in treating patients with severe hypertriglyceridemia, as many are diabetic. *See supra* ¶ 132. Mori 2000 concluded that the changes effected by DHA supplementation "may represent a more favorable lipid profile than seen after EPA supplementation." DX 1538 at ICOSAPENT_DFNDTS00011033, Mori 2000 at 1092. Mori 2000 therefore would have discouraged a person of ordinary skill in the art from eliminating the DHA from LOVAZA®.

c) Hayashi et al., *Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from Fish Oils*, 56 Current Therapeutic Research 24 (1995) ("Hayashi") (DX 1532)

687. Hayashi, another small study, examined the effects of 1.8 g/day of EPA in 28 Japanese patients with baseline triglycerides of at least 150 mg/dl or starting cholesterol levels of at least 220 mg/dl over an 8-week period. DX 1532 at ICOSAPENT_DFNDTS00006161–62, Hayashi at 24–25. Hayashi was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

688. Hayashi was a small, non-blinded, non-placebo-controlled study in patients with "familial combined hyperlipidemia." *Id.* at ICOSAPENT_DFNDTS00006161. The small size and open, uncontrolled nature of the study by itself limits the reliability of its conclusions. Moreover, Hayashi did not disclose the purity of the EPA administered.

689. Hayashi did not report the lipid effects of purified EPA in persons with triglyceride levels of at least 500 mg/dl, and therefore did not teach or create an expectation that high purity EPA would avoid substantial LDL-C increases in persons with very high triglycerides. Indeed, as discussed below, the method used in Hayashi to determine LDL-C levels, the so-called Friedewald Equation, is not valid in individuals whose triglyceride levels exceed 400 mg/dl, and so a person of ordinary skill in the art would understand that the LDL-C values reported in Hayashi could not have come from individuals with triglyceride levels at or above 500 mg/dl.

690. All, or virtually all, of the subjects in Hayashi had triglyceride levels well below 500 mg/dl.

691. Hayashi included correlation graphs in Figure 2, which reported correlations between activities of coagulation factors VII and X and content of plasminogen activator inhibitor-1 (PAI-1) with the plasma triglyceride content of study subjects at week 0. *See id.* at ICOSAPENT_DFNDTS00006165, Figure 2. As shown in these graphs, the highest value on the x-axis (denoting baseline TG levels at week 0) was less than 450 mg/dl. *See id.* Virtually all plot points fell below 350 mg/dl, with most points falling between 150 mg/dl and 350 mg/dl, revealing that the large majority of subjects in the study had triglyceride levels below 350 mg/dl. *See id.* Not a single plot point exceeded 450 mg/dl, let alone 500 mg/dl. *See id.* Figure 2 thus indicated that (1) at the very least, the overwhelming majority of subjects in the study had TG levels below 400 mg/dl; (2) at least 25 of the 28 subjects had TG levels below 450 mg/dl; and (3) there is no clear indication that any subject in the study in fact had TG levels of at least 500 mg/dl. *See id.*

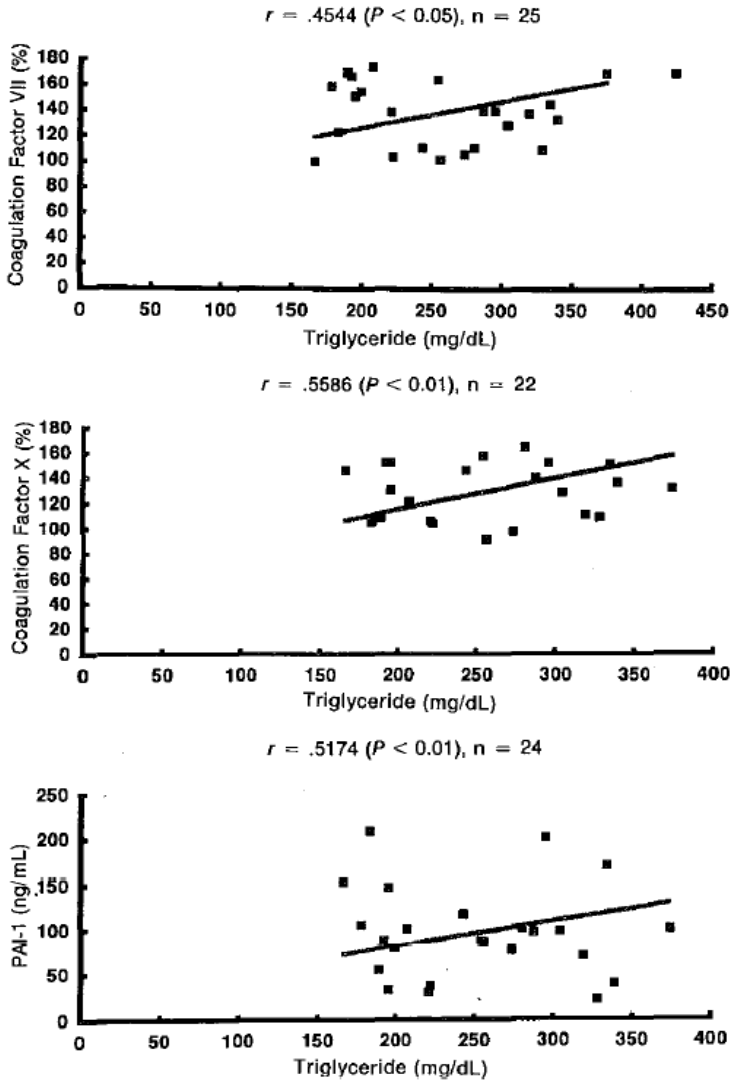

Figure 2. Correlations between activities of coagulation factors VII and X and content of plasminogen activator inhibitor-1 (PAI-1) with plasma triglyceride content at week 0.

692. Figure 2 also raises questions about whether Hayashi was able to obtain triglyceride values for all 28 subjects enrolled in the study. The highest number of subjects reported on the graphs in Figure 2, denoted by "n," was 25 subjects. *See id.* By contrast, results for all 28 subjects in the study were reported in some of the graphs in Figure 1, which reported correlations between activities of coagulation factors VII and X and content of PAI-1 with plasma total cholesterol content at week 0. *See id.* at ICOSAPENT_DFNDTS00006164, Figure 1. That Hayashi reported results based on triglyceride levels for only 25 subjects, rather than all

28 subjects, suggests that the study investigators may have had difficulty measuring the triglyceride levels of the remaining 3 subjects, and that triglyceride levels for those three subjects were unavailable. Indeed, Hayashi specifically noted in Figure 1 that the number of patients included in the results varied "because, in some cases, measurements could not be taken." *Id.*

693. Defendants contend that at least one subject in Hayashi would have had triglyceride levels over 500 mg/dl given that the reported triglyceride mean in Hayashi was 300 ± 233 mg/dl, and that Hayashi therefore would have provided reliable information about the LDL-C effects that highly purified EPA would have had in persons with very high triglycerides. Defendants further contend that the only reason the Patent Examiner issued the Asserted Patents was that the applicants submitted declarations from Dr. Lavin stating that there were no subjects in the Hayashi reference that had triglyceride levels of at least 500 mg/dl, when according to Defendants, there was at least one subject. But, as noted, Figure 2 in Hayashi provided no information about any subject having triglycerides levels of at least 500 mg/dl, and Figure 2 indicated that at least 25 of the 28 study subjects had triglyceride levels below 450 mg/dl. And, as discussed above, the Patent Examiner never stated that the decision to grant the patents depended on the analysis in the Lavin Declarations, and the reasons provided by the Examiner for allowing the claims was unrelated to the analysis provided by Dr. Lavin. *See supra* ¶¶ 662–73.

694. Even if Hayashi had enrolled a few subjects with triglyceride levels of at least 500 mg/dl, moreover, there is no indication that LDL-C data was measured in, or reported for, such subjects in Hayashi. Hayashi provided no breakdown of LDL-C results showing that any of the reported values were taken from persons with triglyceride levels of at least 500 mg/dl, *see* DX 1532 at ICOSAPENT_DFNDTS00006163, Hayashi at 26, Table I, and a person of ordinary skill in the art would have expected that study investigators in Hayashi would not have measured LDL-C in, or included LDL-C results from, any subjects with triglycerides of at least 400 mg/dl.

695. Hayashi reported that LDL-C concentrations in the study were calculated using the Friedewald Equation. *Id.* at ICOSAPENT_DFNDTS00006163. But a person of ordinary

skill would have known that the Friedewald Equation was not a valid way to measure LDL-C in persons with baseline triglyceride levels exceeding 400 mg/dl. *See, e.g.*, DX 1546 at ICOSAPENT_DFNDTS00006797, Saito et al., *Results of Clinical Usage of Improved Formulation (MND-21S) Epadel Capsule 300 with Respect to Hyperlipidemia*, 26 Japan Pharmacology Therapeutics 2047 (1998) ("Saito") at 2050 ("[T]his [Friedewald] formula can't be applied when the TG value is greater than or equal to 400 mg/dL."); PX 1021 at 000007, Rifai et al., *Measurement of Low-Density Lipoprotein Cholesterol in Serum: a Status Report*, 38 Clinical Chemistry 150 (1992) at AMRN-PEXP-0008406 ("Because of increased errors in LDL-C estimation at high triglyceride concentrations, most investigators do not recommend using the Friedewald equation when triglyceride concentrations exceed [400 mg/dl]"); PX 1019 at 000001, Maitra et al., *Comparison of Two Assays for Measuring LDL Cholesterol*, 43 Clinical Chemistry 1040 (1997) ("Maitra") at AMRN-PEXP-0008373 ("The Friedewald formula is still used by most laboratories to estimate LDL-C concentrations. The equation has been clearly shown to be invalid in hypertriglyceridemic patients [triglycerides (Tg) ≥ [400 mg/dl]] …"); PX 1020 at 000007, Nauck et al., *Methods for Measurement of LDL-Cholesterol: A Critical Assessment of Direct Measurement by Homogeneous Assays versus Calculation*, 48 Clinical Chemistry 236 (2002) ("Nauck") at AMRN-PEXP-0008387 ("For individuals with TGs > [400 mg/dl], chylomicrons, or type III HLP [(hyperlipoproteinemias)], the use of the Friedewald equation for LDL-C estimation is not considered valid."); DX 1537 at ICOSAPENT_DFNDTS00006450, Matsuzawa et al., *Effect of Long-Term Administration of Ethylicosapentate (MND-21) in Hyperlipaemic Patients*, 7 J. Clinical Therapeutic Med. 1801 (1991) ("Matsuzawa") (noting that the Friedewald formula "does not apply where triglycerides ≥ 400 mg/dL.").

696. Given that Friedewald was not an appropriate method for measuring LDL-C in such patients, a person of ordinary skill would have understood that the study investigators would have excluded LDL-C measurements from any persons with triglyceride levels of at least 400 mg/dl, and provided LDL-C results only from subjects with TG levels below 400 mg/dl.

697. Indeed, this is precisely what study investigators did in other prior art references cited by Defendants. For example, the Saito reference "treated as missing" LDL-C results from patients with triglycerides levels of at least 400 mg/dl, because the "[Friedewald] formula can't be applied when the TG value is greater than or equal to 400 mg/dL." DX 1546 at ICOSAPENT_DFNDTS00006798, Saito at 2050. Similarly, Matsuzawa observed that the Friedewald formula "does not apply where triglycerides ≥ 400 mg/dL," and on that basis data from subjects with triglycerides of at least 400 mg/dl were excluded from the LDL-C calculation. DX 1537 at ICOSAPENT_DFNDTS00006450, Matsuzawa at 11. Thus, a person of ordinary skill would have understood that LDL-C results reported in Hayashi did not include results from persons with triglyceride levels of at least 400 mg/dl, much less above 500 mg/dl.

698. That the LDL-C results in Hayashi did not include results from persons with triglyceride levels of at least 500 mg/dl is further supported by Figure 2, DX 1532 at ICOSAPENT_DFNDTS00006165, Hayashi at 28. As noted above, no values in Figure 2 included persons with triglycerides of least 500 mg/dl, and the overwhelming majority of plot points fell below 400 mg/dl.

699. Further, even if Hayashi had enrolled a study subject or two with triglyceride levels of at least 500 mg/dl, and even if Hayashi attempted to measure LDL-C for those individuals, a person of ordinary skill would have understood that Hayashi's use of the Friedewald Equation meant that the study could not have provided valid information about the effects of purified EPA on LDL-C in persons with very high TGs.[15]

700. Hayashi did not report the effect of high purity EPA on apoB in persons with triglyceride levels of at least 500 mg/dl. There is no indication that apoB data was measured in, or reported for, any subjects with very high triglycerides, as Hayashi provided no clear indication

[15] In addition, to the extent that any LDL-C results were taken from individuals with triglycerides of at least 500 mg/dl, that number would have been so small that a person of ordinary skill would not have drawn conclusions about the effects of highly purified EPA in the very high triglyceride population.

that any subjects actually had triglyceride levels of at least 500 mg/dl. *See supra* ¶¶ 690–92. Additionally, Hayashi provided no breakdown of apoB results showing that any of the reported values were taken from persons with triglyceride levels of at least 500 mg/dl. *See* DX 1532 at ICOSAPENT_DFNDTS00006163, Hayashi at 26, Table I.

701. Hayashi does not show that EPA reduced apoB even in patients with triglyceride levels below 500 mg/dl after at least 12 weeks of treatment. In Hayashi, the change in apoB was not statistically significant compared to baseline, and the value reported was at week 8, not week 12. *See id.*

702. Hayashi did not express a preference for EPA over DHA. It did not compare EPA to DHA, or demonstrate that EPA had advantages over DHA (in any population). It did not state that DHA would increase LDL-C or that EPA is the only component of fish oil responsible for lowering triglycerides. The authors explained, "the mechanism by which N-3 fatty acids in fish oil decrease plasma cholesterol and triglyceride content is well documented." *Id*. at ICOSAPENT_DFNDTS00006167.

d) Kurabayashi et al., *Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women*, 96 Obstetrics Gynecology 521 (2000) ("Kurabayashi") (PX 376)

703. Kurabayashi assessed the efficacy and safety of a combination therapy of EPA and estriol for the treatment of hyperlipidemia in symptomatic menopausal Japanese women, whose serum cholesterols were 220 to 280 mg/dl or whose serum triglycerides were 150 to 400 mg/dl at baseline. *See* PX 376 at 000001, Kurabayashi at ICOSAPENT_DFNDTS00006237. Patients who were administered EPA had a mean baseline triglyceride level of 136 mg/dl. *Id.* at 000004, Table 2. The study groups were treated with 2 mg daily estriol (72 women) or 1.8 g daily EPA and 2 mg daily estriol (69 women). *See id.* No subjects received EPA alone, and the study did not specify the purity of the EPA administered. Kurabayashi was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

704. Because Kurabayashi did not study subjects with very high TG levels, it would not have altered the expectation that administration of highly purified EPA to persons with very

high triglycerides would produce large increases in LDL-C. Additionally, because Kurabayashi administered EPA in combination with estriol (which was a lipid-altering agent)[16], a person of ordinary skill would not have been able to draw conclusions about the lipid effects of EPA alone—including the effects of EPA alone on LDL-C and apoB.

705. Nor did Kurabayashi disclose that EPA reduced apoB. As noted above, Kurabayashi did not study the effect of EPA alone, but instead looked at the effect of a combination of EPA and estriol (a lipid-altering agent) on lipid parameters of Japanese post-menopausal women with triglycerides below 500 mg/dl. Because Kurabayashi did not study the effect of EPA alone, a person of ordinary skill in the art would not have been able to discern the effect that EPA had on apoB, even in the population that Kurabayashi studied.

706. Kurabayashi measured various blood-lipid parameters at the end of weeks 12, 24, and 48. *See* PX 376 at 000002, Kurabayashi at ICOSAPENT_DFNDTS00006238. After all measured time points, the difference between the apoB value of the group receiving EPA and estriol was not significantly different from the apoB value of the estriol group. *See id.* at 000005, Table 3.

707. To the extent Kurabayashi suggested anything about EPA, it was that EPA is not a particularly effective triglyceride-lowering agent. In Kurabayashi, almost half the subjects in the EPA+estriol group did not show improvement in triglyceride levels. *See id.* at 000003 (reporting that only 55% (11 of 20) in the EPA/estradiol group showed improvement in triglyceride levels). Given the importance of lowering triglycerides in persons with severe hypertriglyceridemia, Kurabayashi would have discouraged the use of purified EPA in persons with triglyceride levels of at least 500 mg/dl.

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[16] *See, e.g.*, PX 1018 at 000001, Itoi et al., *Comparison of the Long-Term Effects of Oral Estriol with the Effects of Conjugated Estrogen on Serum Lipid Profile in Early Menopausal Women*, 36 Maturitas 217 (2000) at AMRN-PEXP-0008328 ("After 48 months of treatment, the [total cholesterol] decreased significantly by 4.3 $\pm$ 2.1% (mean $\pm$ SE) from baseline in the E_3 [estriol] group."); *see also* PX 1012 at 000002–04, Cheng et al., *Prospective Double-Blind Study of CEE3 in Peri- and Postmenopausal Women: Effects on Bone Loss and Lipoprotein Lipids*, 105 Chinese Med. J. 929 (1992) at AMRN-PEXP-0008188–90.

708. Kurabayashi did not compare purified EPA to DHA and did not teach that high purity EPA offered advantages over DHA or a mixture.

e) WO 2008/004900 ("WO '900") (DX 1525)

709. International Patent Application WO 2008/004900, entitled "Production of Ultrapure EPA and Polar Lipids from Largely Heterotrophic Culture," was published in January 2008. As its title suggests, WO '900 focused on *production* of ultrapure EPA, and it described "a process for obtaining an eicosapentaenoic acid (EPA)-rich composition for therapeutic or prophylactic use, wherein the process employs a culture of micro-organisms of a type selected for a capability of largely heterotrophic growth, and a capability of production of EPA, and a capability of photosynthetic lipid production." DX 1525 at ICOSAPENT_DFNDTS00007120, WO '900, ll. 350–54. WO '900 was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

710. Defendants contend that WO '900 taught that high purity EPA has beneficial therapeutic effects, and that DHA was an undesirable molecule that diminished the desired health effect of EPA-rich compositions. But WO '900 focused on the *production* of EPA-rich compositions, and beyond WO '900's teachings about how to produce EPA, a person of ordinary skill in the art would not have found WO '900 to provide useful or credible guidance.

711. That a person of ordinary skill would not have found WO '900 to provide credible instruction about the clinical use of EPA is evident from the laundry list of therapeutic uses it enumerated—a list so long, varied, and unsupported as to be absurd.

> In a further alternative aspect the invention provides for use of a composition, as previously described in this section, in the manufacture of a medicament for treatment of a person affected by certain medical conditions or disorders including but not limited to those selected from diabetes (type I, and type II), glycaemic disorders, diabetes-associated hypertension, cancer, osteoarthritis, autoimmune diseases, rheumatoid arthritis, inflammatory and auto-immune diseases other than arthritis, respiratory diseases, neurological disorders, neurodegenerative disorders (including Huntington's disease, Parkinson's disease, Alzheimer's disease, schizophrenia, major depression, unipolar depression, bipolar depression, obsessive compulsive disorder, borderline personality

> disorder, postnatal depression, organic brain damage, and traumatic brain injury), renal and urinary tract disorders, cardiovascular disorders, cerebrovascular disorders, degenerative diseases of the eye, psychiatric disorders, reproductive disorders, visceral disorders, muscular disorders, metabolic disorders, prostatic hypertrophy and prostatitis, impotence and male infertility, mastalgia, male pattern baldness, osteoporosis, dermatological disorders, dyslexia and other learning disabilities, cancer cachexia, obesity, ulcerative colitis, Crohn's disease, anorexia nervosa, burns, osteoarthritis, osteoporosis, attention deficit/hyperactivity disorder, and early stages of colorectal cancer, lung and kidney diseases, and disorders associated with abnormal growth and development.

DX 1525 at ICOSAPENT_DFNDTS00007124–25, WO '900, ll. 482–96.

712. As of March 2008, a person of ordinary skill would have been highly skeptical that EPA was effective in treating the numerous conditions and diseases listed in WO '900—including impotence, cancer, lung disease, Alzheimer's disease, dyslexia, male pattern baldness, and osteoporosis to name a few. And WO '900's list of conditions and disorders that EPA could supposedly treat was so long and unsupported that a person of ordinary skill in the art would not have lent credence to it (though if such person had, WO '900 would have led them to focus on developing EPA as a treatment for such deadly disorders as cancer or Alzheimer's disease, rather than severe hypertriglyceridemia, which is not even listed in WO '900). Rather, a person of ordinary skill would have concluded from it that WO '900 was not to be taken seriously to the extent it discussed clinical use of EPA.

713. Other statements in WO '900 would have further reinforced that conclusion. Elsewhere, for example, WO '900 made the incredible suggestion, unsupported by data, that EPA had therapeutic benefits for seemingly every system and tissue in the body:

> Preferably the products when consumed are capable of promoting brain and mental health, cognition and behaviour. . . . Preferably the products when consumed are capable of eliciting health promoting effects on any of the following non limiting list of body systems and tissues; auditory, appetite, arousal, balance, blood, bone, bowel, cardiovascular, digestive, endocrine, enteric, emotional, gastric, hair, hepatic, immune, lymphatic, kineaesthetic, marrow, memory, metabolic, musculoskeletal, neurotransmitter, nasopharyngeal,

> pancreatic, musculoskeletal, reproductive, respiratory, ocular, oesophagal, olfactory, palate, pulmonary, proprioceptive, renal, skin, sleep, stomach, sensorimotor, skin, urinogenital, wound healing.

Id. at ICOSAPENT_DFNDTS00007126, ll. 523–28.

714. A person of ordinary skill in the art would have been aware of no evidence that EPA had such a wide range of therapeutic effects, and WO '900 provided none. The statements in this passage would have confirmed to a person of ordinary skill in the art that the clinical statements about EPA in WO '900 were made without care or evidentiary basis, and that WO '900 was not a reliable guide to the therapeutic use of EPA.

715. WO '900 did not mention hypertriglyceridemia, persons with very high triglycerides, the dose or duration for treating such persons, or why EPA would benefit such persons. Nor did it mention LDL-C, or describe a method for avoiding large LDL-C increases in persons with very high triglycerides. The only studies concerning the therapeutic effects of EPA WO '900 cited were Yokoyama & Peet and Horrobin, *id.* at ICOSAPENT_DFNDTS00007113, ll. 125–27, but neither of those references examined the effects of EPA in persons with very high triglycerides. WO '900 therefore provided no suggestion that high purity EPA would lower triglycerides in persons with very high triglycerides without a substantial increase in LDL-C.

716. That WO '900 mentioned treating so many disorders with high purity EPA—but nowhere mentioned using high purity EPA to lower triglycerides in persons with hypertriglyceridemia—demonstrates that it was not obvious to use high purity EPA to lower triglycerides in persons with very high triglycerides.

717. There is also no discussion or evidence in WO '900 of why DHA would be undesirable in treating hypertriglyceridemia. WO '900 only vaguely and generically stated without evidence that "the desired effects of EPA are limited or even reversed by the co-consumption of undesired molecules; … in particular docosahexaenoic acid (DHA) …." *Id.* at ll. 130–33. Especially given the absence of any identified particular concern with use of DHA in the context of treating persons with very high triglycerides, or supporting evidence, a person of ordinary skill in the art would not have been influenced by WO '900's statements about the

relative benefits of EPA and DHA. More generally, given that WO '900's statements about the clinical effects of EPA were not credible, a person of ordinary skill in the art would not have even looked to WO '900 if seeking to make an improved omega-3 fatty acid treatment for hypertriglyceridemia.

f) Epadel Prescribing Information (2007) ("Epadel PI 2007") (DX 1528)

718. Epadel PI 2007 is the prescribing information for Epadel Capsules 300, a Japanese product of high purity EPA from 2007. Epadel PI 2007 was the fifth version of the prescribing information. An earlier version of the Epadel prescribing information was included in the second edition of the Japan Pharmaceutical Reference in 1991–1992. *See* DX 1527, Epadel Capsules 300, Japan Pharmaceutical Reference 369 (2d ed. 1991) ("Epadel JPR"). But notwithstanding the fact that highly purified EPA had been known since the early 1990s, no one had developed a method of lowering triglycerides in persons with severe hypertriglyceridemia using high purity EPA as of March 2008. Epadel PI 2007 was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

719. Epadel PI 2007 stated that Epadel was indicated for "Arteriosclerotic ulceration, alleviation of pain and feeling cold" and "Hyperlipidemia." DX 1528 at ICOSAPENT_DFNDTS00008962, Epadel PI 2007. The "Clinical Results" section disclosed that "in long term administration (24–52 weeks) serum total cholesterol was reduced by 3–6% … and serum triglycerides was reduced 14–20% (in 97 cases where it was greater than 150 mg/dl before administration) and that effect was stable." *Id*. at ICOSAPENT_DFNDTS00008966.

720. Epadel PI 2007 did not describe lowering triglycerides in persons with triglyceride levels of at least 500 mg/dl. Nor did it report the LDL-C effects of purified EPA in any population, let alone persons with very high triglycerides. It therefore did not disclose that highly purified EPA reduces triglycerides in persons with very high triglycerides without a substantial increase in LDL-C. Nor did the Epadel PI 2007 describe the effects of high purity EPA on apoB in any population.

721. Epadel PI 2007 did not teach administering daily doses of 4 g per day of EPA for hypertriglyceridemia. For hyperlipidemia, Epadel PI 2007 prescribed daily dosages of 1.8 to 2.7 grams per day. It generally recommended that 2 capsules of 600 mg EPA three times daily (for a total of 1.8 g per day), but stated that "when an excess of triglycerides are presented, depend[ing] on the extent of it, the dosage may be increased to 900 mg per time and three times daily," for an upper daily dosage of 2.7 g/day. *Id*. at ICOSAPENT_DFNDTS00008962.

2. Summary of other selected prior art references

722. Amarin will present several additional prior art references, some of which are addressed below:

a) Agren et al., *Fish Diet, Fish Oil and Docosahexaenoic Acid Rich Oil Lower Fasting and Postprandial Plasma Lipid Levels*, 50 European J. Clinical Nutrition 765 (1996) ("Agren") (PX 918)

723. Agren investigated the effects of fish diet, fish oil, and DHA-rich oil on lipid levels in healthy male subjects. Agren was a randomized single-blind study involving 59 subjects. PX 918 at 00003–04, Agren at AMRN00289898–99. The subjects were randomly allocated into control, fish diet, fish oil, and DHA-oil groups. *Id.* at 000005. The fish diet group received 4.3 fish-containing meals per week providing 0.38 g EPA and 0.67 g DHA per day. *Id.* The fish oil group received 4 g fish oil per day providing 1.33 g EPA and 0.95 g DHA per day. *Id*. The DHA-oil group received 4 g DHA-oil per day providing 1.68 g DHA per day. *Id*. at 000004. The subjects in the control group did not take any supplements. *Id.* Agren was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

724. Agren observed that "[n]o tendency to increased LDL cholesterol was seen in the DHA-oil group." *Id.* at 000008. The DHA-oil group's mean LDL-C level was 2.49 mmol/L (96.3 mg/dl) at the beginning of the study, and it decreased to 2.42 mmol/L (93.6 mg/dl) after 14 weeks. *Id.* at 000007, Table 3.

725. Agren stated that "a study comparing oils with different EPA to DHA ratios indicates that only oil rich in DHA can decrease LDL cholesterol and is better at maintaining

HDL concentrations than oils rich in EPA," and that "[i]n accordance with earlier results, a moderate n-3 fatty acid intake in the present study did not show any significant changes in LDL cholesterol concentrations, although a slight increasing tendency was seen in the fish diet and fish oil groups." *Id.* at 000003, 000007.

726. Agren also showed that DHA improved the HDL to LDL cholesterol ratio. The DHA-oil group's HDL to LDL cholesterol increased from 0.55 to 0.64 in 14 weeks with $P < 0.05$ compared to the control group. *Id.* at 000005. Agren stated that "the HDL to LDL cholesterol ratio was increased only in [the DHA-oil] group." *Id.* at 000008.

b) Conquer & Holub, *Supplementation with an Algae Source of Docosahexaenoic Acid Increases (n-3) Fatty Acid Status and Alters Selected Risk Factors for Heart Disease in Vegetarian Subjects*, 126 J. Nutrition 3032 (1996) ("Conquer") (PX 920)

727. Conquer reported results of a double-blind study that investigated the influence of dietary supplementation with an algae source of DHA on serum/platelet DHA status, the estimated retroconversion of DHA to EPA, and risk factors for heart disease in vegetarian subjects. PX 920 at 000001, Conquer at AMRN00290326. Twenty-four healthy vegetarians were randomly assigned to two groups—DHA-supplemented and control. *Id*. at 000002. The DHA-supplemented group consumed capsules containing 1.62 g/day DHA, whereas the control group received vegetable placebo capsules. *Id*. Conquer was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

728. In Conquer, "no significant alteration was found in the total- and LDL-cholesterol levels with DHA supplementation." *Id*. at 000004. The DHA-supplemented group's LDL-C decreased from 1.99 mmol/L (77.0 mg/dl) at baseline to 1.86 mmol/L (71.9 mg/dl) at the study end. *Id.* at 000005, Table 4. Conquer commented that past clinical trials with fish oils that often increased LDL-C "have employed fish oil concentrates which usually contain much more EPA than DHA." *Id.* at 000006.

729. Conquer reported with DHA "a significant decrease in the total cholesterol:HDL-cholesterol ratio (by 16%) as well as the LDL-cholesterol:HDL-cholesterol ratio (by 22%)." *Id.*

at 000004. "These changes are consistent with a favorable influence of dietary DHA on these recognized lipid/lipoprotein risk factors for cardiovascular disease." *Id.* at 000006. In contrast, "[s]upplementation with fish oils containing EPA plus DHA for several weeks has generally not significantly reduced LDL-cholesterol:HDL-cholesterol ratios." *Id.*

730. Conquer noted that recent studies had suggested that DHA has cardioprotective effects, observing "an inverse relationship between DHA levels in the population (both diet and blood) and the risk of CVD," and that "part of the cardioprotective effect of fish/fish oils containing (n-3) PUFA appears due to DHA in addition to EPA." *Id.* at 000006-07. Conquer also noted that DHA's antiarrhythmic effect "may account for the reduction in cardiac arrest and sudden cardiac death in those having a higher DHA status." *Id.* at 000007.

731. Conquer concluded that the consumption of 1.62 g of an animal-free source of DHA per day "exerts moderately favorable (lowering) effects on the total cholesterol:HDL-cholesterol ratio, the LDL-cholesterol:HDL-cholesterol ratio, as well as serum triglyceride concentrations." *Id.*

c) Grimsgaard et al., *Effects of Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid on Hemodynamics in Humans,* 68 Am. J. Clinical Nutrition 52 (1998) ("Grimsgaard 1998") (PX 1028)

732. Grimsgaard 1998, investigated in a randomized, double-blind, parallel-design intervention study the separate effects of EPA and DHA on blood pressure, heart rate, and cardiac mechanics in 224 healthy non-smoking men. PX 1028 at 000001, Grimsgaard 1998 at ICOSAPENT_DFNDTS00009272. Randomized subjects received either 4 g/day of DHA, 4 g/day of EPA, or corn oil. *Id*. Grimsgaard 1998 was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

733. Grimsgaard 1998 observed that heart rate decreased in persons administered DHA while increasing in the group who took EPA. *Id.* at 000003. ("Compared with the control group, heart rate in the DHA group decreased and that in the EPA group increased across all values of baseline heart rate.").

d) Mori et al., *Docosahexaenoic Acid but Not Eicosapentaenoic Acid Lowers Ambulatory Blood Pressure and Heart Rate in Humans,* 34 Hypertension 253 (1999) ("Mori 1999") (PX 565)

734. Mori 1999, published in 1999, investigated whether there were significant differences in the effects of purified EPA or DHA on ambulatory blood pressure (BP) and heart rate (HR) in humans. PX 565 at 000002, Mori 1999 at AMRN01177186. Mori 1999 was a double-blind, placebo-controlled trial of parallel design in which 59 overweight, mildly hyperlipidemic men were randomized to 4 g/day of purified EPA, DHA, or olive oil for 6 weeks. *Id.* Mori 1999 was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

735. Mori 1999 observed that "purified DHA, but not EPA, resulted in a significant reduction in [ambulatory] BP and HR compared with placebo." *Id*. at 256. The authors concluded that DHA may be the principal ω3 fatty acid in fish and fish oils that lowers BP and HR in humans. *Id*. at 000008.

e) Rambjør et al., *Eicosapentaenoic Acid Is Primarily Responsible for Hypotriglyceridemic Effect of Fish Oil in Humans,* 31 Lipids S-45 (1996) ("Rambjør") (PX 561)

736. Rambjør investigated the effects of EPA and DHA on lipid and lipoprotein levels in 49 normolipidemic subjects. Rambjør reported data obtained from three separate studies in which subjects took 3 g/day EPA, 3 g/day DHA, or 5 g/day fish oil concentrate for three weeks prior to or after taking 5 g/day olive oil placebo. PX 561 at 000003, Rambjør at AMRN00290976. Rambjør was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

737. In Rambjør, both fish oil concentrate and EPA significantly increased LDL-C levels, and reduced triglycerides. *Id.* at 000004, 000005, Table 3. On the other hand, DHA did not raise LDL-C by a statistically significant amount. *Id.* Rambjør also observed that a previously reported study "concluded that both EPA and DHA were equally hypotriglyceridemic, but that DHA also lowered LDL, while EPA did not." *Id.* at 000004. In Rambjør, DHA did not affect triglyceride levels. *Id.* at 000003.

738. DHA also had a favorable effect on HDL_2-C levels. Both fish oil concentrate and DHA significantly increased HDL_2-C levels. *Id.* at 000005, Table 3. EPA had no such effect. *Id.* "HDL_2-C levels have been inversely associated with coronary heart disease." *Id.* at 000005. "Thus, n-3 FA-induced increase in this HDL subfraction may contribute to the antiatherogenic potential of fish oils." *Id.*

f) von Schacky, A Review of Omega-3 Ethyl Esters for Cardiovascular Prevention and Treatment of Increased Blood Triglyceride Levels, 2 Vasc. Health Risk Manag. 251 (2006) ("von Schacky") (PX 905)

739. von Schacky, published in 2006, reviewed prior studies that investigated the effects of DHA and EPA on cardiovascular prevention and treatment of hypertriglyceridemia. PX 905 at 000001, von Schacky at AMRN-PEXP0007466. von Schacky was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

740. As part of his review, von Schacky recounted what the art had reported about the serum lipid effects of DHA-EPA mixtures on serum lipids, observing that a combination of EPA and DHA lowered triglycerides; increased HDL in some studies (up to 15%) but not in others; had no meaningful effect on glucose metabolism; lowered blood pressure; improved endothelial function, and "prevent[ed] occlusion of arterial grafts, be it venous or polytetrafluoroethylene." *Id.* at 000003–04, 000006–07. With respect to LDL-C, von Schacky reported that with an EPA-DHA combination, "[r]ather consistently, LDL has been seen to be increased." *Id*. at 000005.

741. von Schacky also reported effects of purified EPA vs. DHA, reporting with respect to LDL-C that EPA and DHA had similar effects. *See id*. ("In more recent comparative studies, no effects of either EPA or DHA were seen on total cholesterol, HDL, or LDL."). von Schacky also observed that purified DHA had various advantages over EPA in terms of cardioprotective effects. "DHA, but not EPA, increased LDL particle size." *Id.* "DHA appears more effective in terms of inhibition of platelet aggregability than EPA." *Id.* at 000006. "[H]eart rate was reduced by DHA … , whereas EPA did not have an effect." *Id*. "[B]lood pressure is lowered by DHA, but not by EPA." *Id.* "[T]he available evidence indicates that

EPA-DHA improve endothelial function in patients with cardiovascular disorders. When compared, DHA, but not EPA was found to be effective." *Id.* at 000007.

742. von Schacky also summarized observations about DHA and EPA in a table, *see id.* at 000009, Table I:

Table I Effects of purified eicosapentaenoic and docosahexaenoic acid, as observed in human studies, only significant differences were considered for inclusion. Arrows reflect semi-quantitatively the findings from the literature

	EPA	DHA
Triglycerides	↓↓	↓↓
Cholesterol	↔	↔
LDL	↑	↑
HDL	↔?	↑?
platelet aggregability	(↓)	↓
mean platelet volume	↓	↔
blood pressure	↔	↓
heart rate	↓	↓↓
endothelial function	↔	↑
glucose metabolism	↔	↔

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Note: Information sourced from von Schacky and Weber 1985; Nozaki et al 1992; Rambjor et al 1996; Grimsgaard et al 1997, 1998; Mori, Bao, et al 1999; Mori, Burke, et al 2000; Mori, Watts, et al 2000; Woodman et al 2000, 2002, 2003a, 2003b; Park and Harris 2002; Mori and Woodman 2006.

743. The table reported that DHA and EPA had similar effects of increasing LDL-C, and that DHA was understood to have advantages over EPA in terms of effects on HDL, platelet aggregability, blood pressure, heart rate, and endothelial function. *See id*.

g) Woodman, et al., *Effects of Purified Eicosapentaenoic Acid and Docosahexaenoic Acid on Platelet, Fibrilolytic and Vascular Function in Type 2 Diabetic Patients,* 166 Atherosclerosis 85 (2003) ("Woodman 2003a") (PX 564)

744. Woodman 2003a, published in 2003, reported results from a double-blind placebo-controlled trial that investigated whether purified EPA or DHA from fish oil have differential effects on platelet, fibrinolytic, and vascular function in patients with Type 2 diabetes

and hypertension. PX 564 at 000001, Woodman 2003a at AMRN01172851. Subjects received 4 g/day of EPA, 4 g/day DHA, or olive oil for 6 weeks. *Id*. Woodman 2003a was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

745. Woodman 2003a reported collagen-induced platelet aggregation and TXA_2 (thromboxane A2) release reductions with DHA but not EPA supplementation. *Id*. at 000006. Woodman 2003a further stated that "highly purified DHA may be a more effective anti-thrombotic agent than EPA," *id*. at 000001, and that its results suggested that "DHA has inhibitory effects on platelet function." *Id*. at 000008. The study concluded that "[i]n conjunction with the antiarrhythmic, lipid lowering (in press) and anti-inflammatory effects of DHA, the results indicate that DHA may be useful in the treatment of Type 2 diabetic subjects with treated hypertension." *Id*.

h) Woodman, et al., *Docosahexaenoic Acid but Not Eicosapentaenoic Acid Increases LDL Particle Size in Treated Hypertensive Type 2 Diabetic Patients*, 26 Diabetes Care 253 (2003) ("Woodman 2003b") (PX 563)

746. Woodman 2003b, published in 2003, reported additional data from the Woodman 2003a study on the differential effects of EPA and DHA on LDL particle size in hypertensive type 2 diabetic subjects. PX 563 at 000001, Woodman 2003b at AMRN01066627. Woodman 2003b observed that LDL particle size increased after supplementation with DHA, but not EPA, in confirmation of the findings in Mori 2000. *Id.* In review of the prior art, Woodman 2003b noted that "[s]upplementation with purified DHA increases LDL particle size, reduces serum triglycerides, and increases HDL_2 cholesterol, as well as improves vascular function and blood pressure." *Id*. The study concluded that for subjects with type 2 diabetes, "DHA may have more therapeutic value than EPA as a food additive." *Id*.

i) Center for Drug Evaluation and Research, FDA, *Approval Package for Application Number 21-654, Statistical Review* (2004) ("LOVAZA® Statistical Review") (PX 939)

747. The LOVAZA® Statistical Review summarized FDA's review of the statistical aspects of the clinical trial data submitted in support of the New Drug Application for

LOVAZA®, which at the time of the review was known as OMACOR®. The LOVAZA® Statistical Review was finalized on October 17, 2004 and was prior art as of March 2008. The LOVAZA® Statistical Review was considered by the United States Patent and Trademark Office during the prosecution of the Asserted Patents.

748. The LOVAZA® Statistical Review contained results from various clinical studies of LOVAZA®, including "Category 1" studies, which were double-blinded, parallel, placebo-controlled studies or parts of studies in patients with hypertriglyceridemia which used 4 g/day of K85 (the name of the study drug, i.e., LOVAZA®). *See id.* at 000005. Among such studies, the U.S. studies (K85-94010 and K85-95009) examined the effect of LOVAZA® in patients who had TG levels of at least 500 mg/dl. *See id.* On the other hand, the European studies (CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, and CK85-023) involved patients with the median TG levels below 500 mg/dl. *See id.*

749. In the LOVAZA® Statistical Review, the reviewer noted that "the median increase in LDL percent change from baseline was greater in the 2 US studies in severe hypertriglyceridemia than in the European studies." *See id.* at 000006. In the U.S. studies, whose patients had the median TG level of 816 mg/dl, LDL-C increased by 44.5% from baseline and by 49.3% compared to placebo. *See id.*, Table 2. In comparison, in the European studies, whose patients had the median baseline TG level of 275 mg/dl, the patients' LDL-C increased only by 4.5% from baseline and by 6.9% compared to placebo. *See id.*

750. The LOVAZA® Statistical Review also showed that LOVAZA® did not reduce apoB in very high TG patients. In the LOVAZA® Statistical Review, the apoB data for the treatment group and the placebo group were presented side-by-side in box plots as percent changes from the baseline apoB levels. *See id.* at 000025, Figure 7, 000033, Figure 14. Among the U.S. studies in the LOVAZA® Statistical Review examining very high triglyceride patients, the apoB data were available only for the K85-95009. *See id.* at 0000033, Figure 14. Therefore, the box plots from pooled U.S. studies in Figure 7 and the K85-95009 study in Figure 14 contained the same data. *See id.* at 0000025, Figure 7, 0000033, Figure 14. These box plots

showed that the median percent change in apoB was slightly negative for the placebo group, meaning that apoB decreased for the placebo group. *See id.* In contrast, the median percent change was close to 0% for the group that received 4 g/day of K85 (LOVAZA®). *See id.* These data showed that apoB remained virtually unchanged compared to baseline in very high TG patients who received LOVAZA®, and that LOVAZA® *increased* apoB in those patients compared to placebo.

751. In addition, the LOVAZA® Statistical Review showed that LOVAZA® reduced non-HDL-C in patients with triglycerides of at least 500 mg/dl. The LOVAZA® Statistical Review presented the non-HDL-C data in box plots like with the apoB data. *See id.* at 0000022, Figure 4, 0000029, Figure 11. The box plots showed that non-HDL-C decreased compared to baseline in each of the K85-94010 and K85-95009 studies, *see id.* at 28, Figure 11, and also for both of the studies combined. *See id.* at 000022, Figure 4. Moreover, the non-HDL-C reductions observed in the patients who received K85 (LOVAZA®) were greater compared to any reduction observed in the patients who received placebo. *See id.* at 000022, Figure 4, 000029, Figure 11. These data show that non-HDL-C does not track apoB in patients with very high triglycerides.

j) Center for Drug Evaluation and Research, FDA, *Approval Package for Application Number 21-654, Medical Review* (2004) ("LOVAZA® Medical Review") (PX 1030)

752. The LOVAZA® Medical Review summarized FDA's review of the medical information in the clinical trial data submitted in support of the New Drug Application for LOVAZA®, which at the time of the review was known as OMACOR®. The Medical Reviewer completed her review on October 1, 2004. *See* PX 1030 at 000002, LOVAZA® Medical Review at PW-AMRN00003915. This was prior art as of March 2008. The LOVAZA® Medical Review was considered by the United States Patent Office during prosecution of the Asserted Patents.

753. The LOVAZA® Medical Review contained results from various clinical studies of LOVAZA®, including "Category 1" studies, which were double-blinded, parallel, placebo-controlled studies or parts of studies in patients with hypertriglyceridemia which used 4 g/day of

K85 (the name of the study drug, *i.e.*, LOVAZA®) *See id.* at 000016. Among such studies, the U.S. studies (K85-94010 and K85-95009) examined the effect of LOVAZA® in patients who had triglyceride levels of at least 500 mg/dl. *See id.* at 000025–26. On the other hand, the European studies (CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, and CK85-023) involved patients with the median triglyceride levels below 500 mg/dl. *See id.*

754. In the LOVAZA® Medical Review, the reviewer noted that 4 g of LOVAZA® had "a more favorable effect on the overall lipoprotein profile . . . only in the Type V patient population defined by the applicant as those patients having triglyceride (Tg) levels ≥ 750 mg/dL." *Id.* at 000006. The reviewer recommended approval of LOVAZA® as an adjunct to diet to reduce triglyceride levels in patients with elevated TG levels of Type V dyslipidemia. *See id.*

755. The results for K85-94010 and K85-95009—the studies with patient populations having triglyceride level of at least 500 mg/dl—showed that most subjects in these trials experienced LDL-C increases.

Table 22. Changes in VLDL-C, ApoB, and Non-HDL-C from Baseline in the K85 4g-treated patients who had INCREASES (↑ LDL) or NO increase (Ø LDL) in LDL-C from baseline

	CK85-013		CK85-014		CK85-017		CK85-019		CK85-022		CK85-023		K85-94010		K85-95009	
baseline Tg for K85 4 g group mean median	308.2 mg/dL 299 mg/dL		294.5 mg/dL 264.5 mg/dL		305.8 mg/dL 276 mg/dL		295.6 mg/dL 267.5 mg/dL		343.5 mg/dL 279 mg/dL		358.3 mg/dL 294.5 mg/dL		840.1 mg/dL 810.5 mg/dL		919 mg/dL 817.5 mg/dL	
	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL	↑ LDL	ØLDL
n	11	1	29	17	18	5	18	8	16	12	10	14	13	6	17	3
relative chg (%) in VLDL-C mean median	ND	ND	ND	ND	ND	ND	-25.8 -26.9	-17.1 -20.4	-27.5 -30.8	-13.6 -16.2	ND	ND	-30.4 -35.2	-22.2 -15.7	-48.2 -49.5	+70.7 +50.5
relative chg (%) in apoB mean median	+8.28 +9.09	-13.75 -13.75	+9.573 +4.0	-3.459 -0.917	ND	ND	+4.50 +2.724	-3.04 0	+8.53 +5.22	-8.37 -6.51	+9.04 +4.52	-4.36 -3.69	ND	ND	+2.86 +0.781	-3.27 -3.36
relative chg (%) in non-HDL-C mean median	+5.1 +4.36	-39.2 -39.2	+9.0 +7.1	-11.5 -12.6	+7.5 +4.7	-30.5 -25.3	+2.6 -0.2	-8.9 -9.8	+8.2 +2.7	-13.4 -14.5	+8.2 +2.7	-13.4 -14.5	-7.3 -6.5	-24.9 -26.1	-18.9 -15.5	-1.2 -2.1

Id. at 0000034, Table 22.

756. In K85-94010, 13 of 19 subjects experienced LDL-C increases. *See id.* And in K85-95009, 17 out of 20 experienced LDL-C increases, with those subjects also experiencing a mean increase of 2.86% in apoB. *See id.*

757. The results in this table would have confirmed to a person of ordinary skill in the art that non-HDL-C did not track apoB in these patients. For example, while subjects in K85-95009 who experienced LDL-C increases experienced *decreases* in non-HDL-C (a mean reduction of 18.9%), those same subjects experienced *increases* in apoB (a mean increase of 2.86%).

758. The LOVAZA® Medical Review also reported that, "[o]verall, patients treated with K85 [(LOVAZA®)] who had an increase in LDL-C from baseline also had mean increases in apoB lipoproteins." *Id.* at 000032. Because a person of ordinary skill in the art would have known that most persons with very high triglycerides experienced increases in LDL-C when taking LOVAZA®, a person of ordinary skill would have understood that most such persons would also experience increases in apoB.

C. Overview of Defendants' Obviousness Combinations

759. While Defendants' obviousness combinations vary somewhat, they are fundamentally similar. Defendants contend that the Asserted Claims would have been obvious over a combination of at least the LOVAZA® PDR and Mori 2000, and for a number of the Asserted Claims, Defendants further combine—sometimes optionally—Hayashi, Kurabayashi, and/or WO '900.

760. Defendants also propose additional alternative combinations for a subset of the Asserted Claims—in particular, the asserted claims of the '560 and '929 patents. These combinations include the same references as noted above, but also include Epadel PI 2007.

761. The Asserted Claims were not obvious over Defendants' obviousness combinations.

XXV. CLAIM 1 OF THE '728 PATENT WAS NOT OBVIOUS

762. Defendants contend that Claim 1 of the '728 patent would have been obvious in March 2008 over the LOVAZA® PDR and Mori 2000, and optionally in further combination with Hayashi and Kurabayashi. Defendants will likely argue that a person of ordinary skill would have understood that LOVAZA® would reduce triglyceride levels in persons with very high triglycerides, but would have sought to modify LOVAZA® to avoid the large LDL-C increases it caused in patients with very high triglycerides. Defendants may further argue that a person of ordinary skill would have understood from Mori 2000, Hayashi, and Kurabayashi that DHA was responsible for LOVAZA®'s LDL-C increases, and therefore would have been motivated to replace the method in the LOVAZA® PDR—*i.e.,* 4 g/day of a combination of EPA and DHA—with 4 g/day high purity EPA, with a reasonable expectation that such treatment would reduce triglycerides without substantially raising LDL-C levels in persons with very high triglycerides. Finally, Defendants will likely contend that, at a minimum, using purified EPA to treat patients with triglycerides of at least 500 mg/dl would have been obvious to try.

763. While large increases in LDL-C caused by LOVAZA® in the very high TG population were undesirable, and a person of ordinary skill would have wanted to find a TG-lowering method that avoided such increases, such a person would not have been motivated to use highly purified EPA (at least 96% by weight with substantially no DHA) to lower triglycerides in persons with very high triglycerides, or reasonably expected success in doing so without substantially raising LDL-C. Nothing in Defendants' obviousness combination establishes otherwise.

764. None of the references in Defendants' combination reported the LDL-C effects of highly purified EPA in a population with fasting triglycerides of at least 500 mg/dl, and therefore would not have altered the strong expectation as of March 2008 that administering highly purified EPA to persons with very high triglycerides would produce large increases in LDL-C. And far from motivating a person of ordinary skill to use highly purified EPA and substantially no DHA, the references in Defendants' combination would have done *the opposite,* making

purified EPA appear less desirable than DHA or a mixture. For these and other reasons—discussed more fully below—Claim 1 of the '728 patent would not have been obvious.

A. Defendants' combination would not have altered the strong expectation that highly purified EPA would produce large LDL-C increases in individuals with very high triglycerides

765. In March 2008, a POSA would have understood that omega-3 fatty acids dramatically increased LDL-C in persons with very high TGs. *See supra* ¶¶ 115–16. A POSA would have believed that this increase was a necessary result of the way in which omega-3 fatty acids lowered TGs in persons with very high TGs. *See id*.

766. The experience with LOVAZA®, which caused large, statistically significant increases in LDL-C when administered to patients with very high triglycerides, and with fibrates, which also produced large LDL-C increases in such patients, and were understood to lower triglycerides through similar mechanisms to omega-3 fatty acids, would have confirmed this belief. *See id*.

767. A POSA would not have ascribed LOVAZA®'s dramatic rise in LDL-C in persons with very high triglycerides to only EPA or only DHA, but instead to both compounds. If a POSA in March 2008 had contemplated the effect of purified EPA alone in persons with very high TGs, that POSA would have expected that EPA would produce large increases in LDL-C.

768. Nothing in Defendants' combination would have altered that expectation. The only references in Defendants' combinations that studied effects of highly purified EPA on LDL-C were in persons with triglyceride levels lower than 500 mg/dl, and a POSA would have understood that such studies were not predictive of the LDL-C effects in persons with TG levels of at least 500 mg/dl.

769. ***LOVAZA® PDR***. LOVAZA® PDR is the only reference in Defendants' proposed combination directed to lowering triglycerides in individuals with triglyceride levels of at least 500 mg/dl, but LOVAZA® is a mixture of DHA and EPA (465 mg EPA, 375 mg DHA per capsule), and the LOVAZA® PDR did not attribute the dramatic increase in LDL-C in persons

with very high TGs to either just DHA or just EPA. Both are described as lowering triglycerides, and both would have been understood as contributing to the rise in LDL-C in persons with very high triglycerides.

770. ***Mori 2000***. Mori 2000 reported results from a double-blind, placebo-controlled trial of parallel design comparing the effects of 4 g/day EPA versus 4 g/day DHA in a small study of 59 overweight mildly hypercholesterolemic men. DX 1538 at ICOSAPENT_DFNDTS00011027, Mori 2000 at 1086.

771. In Mori 2000, the mean baseline TG concentration for patients administered EPA was 178 mg/dl (2.01 mmol/L), and 199 mg/dl (2.25 mmol/L) for patients administered DHA. DX 1538 at ICOSAPENT_DFNDTS00011029, Mori 2000 at 1088, Table 2. Those triglyceride levels are well below 500 mg/dl, and would not have been understood to be predictive of the LDL-C effects of purified EPA in persons with TG levels of at least 500 mg/dl.

772. In Mori 2000, both DHA and EPA increased LDL-C levels (8% increase with DHA vs. 3.5% increase with EPA). That the LDL-C increase with EPA in Mori 2000 was not statistically significant would not have changed that conclusion, as a person of ordinary skill would have attributed the lack of statistical significance with EPA to the fact that the sample size in Mori 2000 was quite small with purified EPA being administered to only 19 subjects. *See Id.*

773. Moreover, a POSA would have believed that the somewhat smaller increase in LDL-C with EPA in Mori 2000 might be attributable to the fact that the baseline triglyceride levels were approximately 11 percent lower in the EPA group than the DHA group, *see id.*, since LDL-C increase was understood to be greater as baseline triglyceride levels increased. *See, e.g.*, PX 923 at 000005, McKenney 2007 II at AMRN00290743.

774. This reading of Mori 2000 (that both EPA and DHA increased LDL-C) would have been confirmed by a subsequent 2006 review publication by von Schacky. After reviewing Mori 2000 and other prior art, von Schacky concluded that both EPA and DHA increased LDL-C. *See* PX 905 at 000009, von Schacky at AMRN-PEXP-0007474, Table I.

775. ***Hayashi***. Hayashi examined the effects of 1.8 g/day of EPA in 28 Japanese patients with baseline TGs of at least 150 mg/dl or starting cholesterol levels of at least 220 mg/dl. DX 1532 at ICOSAPENT_DFNDTS00006161–62, Hayashi at 24–25.

776. Hayashi was a small, non-blinded, non-placebo-controlled study in patients with "familial combined hyperlipidemia." The small size and open, uncontrolled nature of the study by itself limits the reliability of its conclusions.

777. Moreover, as discussed above, all—or virtually all—of the subjects in Hayashi had triglyceride levels well below 500 mg/dl, and a person of ordinary skill would have understood that the LDL-C results reported in Hayashi were not predictive of purified EPA's LDL-C effects in persons with very high triglycerides. *See supra* ¶¶ 689–92.

778. As discussed above, even if there were a few subjects in Hayashi with triglyceride levels of at least 500 mg/dl, a person of ordinary skill would have understood that the study investigators would not have measured LDL-C results for such subjects, and that any such results would have been unreliable. *See supra* ¶¶ 694–99.

779. The data in Hayashi indicated that (1) at the very least, the overwhelming majority of subjects in the study had TG levels below 400 mg/dl; (2) at least 25 of the 28 subjects had TG levels below 450 mg/dl; and (3) there is no clear indication that any subject in the study in fact had TG levels of at least 500 mg/dl. *See id*. And even if Hayashi had enrolled a few subjects with TG levels of at least 500 mg/dl, Hayashi provided no breakdown of LDL-C results showing that any of the reported values were taken from persons with triglyceride levels of at least 500 mg/dl, *see* DX 1532 at, Hayashi at ICOSAPENT_DFNDTS00006163, Table I.

780. Moreover, Hayashi reported that LDL-C concentrations in the study were calculated using the Friedewald Equation. *Id*. at ICOSAPENT_DFNDTS00006163. But a person of ordinary skill would have known that the Friedewald equation was not a valid way to measure LDL-C in persons with baseline triglyceride levels exceeding 400 mg/dl. *See supra* ¶¶ 695–97. Given that Friedewald was not an appropriate method for measuring LDL-C in such patients, a person of ordinary skill would have understood that the study investigators would

have excluded LDL-C measurements from any persons with triglyceride levels of at least 400 mg/dl, and provided LDL-C results only from subjects with triglyceride levels below 400 mg/dl. *See id.* Thus, a person of ordinary skill would have understood that LDL-C results reported in Hayashi did not include results from persons with triglyceride levels of at least 400 mg/dl, much less above 500 mg/dl.

781. ***Kurabayashi***. Kurabayashi assessed the efficacy and safety of a combination therapy of EPA and estriol for the treatment of hyperlipidemia in symptomatic menopausal Japanese women, whose serum triglycerides were 150 to 400 mg/dl at baseline. The study groups were treated with 2 mg daily estriol (72 women) or 1.8 g daily EPA and 2 mg daily estriol (69 women). PX 376 at 000001, Kurabayashi at ICOSAPENT_DFNDTS00006237. No subjects received EPA alone, and the study did not specify the purity of the EPA administered.

782. Kurabayashi did not study subjects with very high triglyceride levels, and therefore would not have altered the expectation that administration of highly purified EPA to persons with very high triglycerides would produce large increases in LDL-C. *See supra* ¶¶ 703–04.

783. Because in Kurabayashi, EPA was administered in combination with estriol (which was a lipid altering agent), a person of ordinary skill would not have been able to draw conclusions about the lipid effects of EPA alone. *See supra* ¶ 704.

B. Defendants' combination would not have motivated a person of ordinary skill to use highly purified EPA and substantially no DHA in persons with very high triglycerides

784. Defendants contend that Mori 2000, Hayashi, and Kurabayashi—three EPA studies—would have motivated a person of ordinary skill to substitute 12 weeks of administration of 4 g/day of a combination of EPA and DHA—*i.e.*, the method disclosed in the LOVAZA® PDR—with 12 weeks of administration of 4 g/day of high purity EPA. Far from motivating a person of ordinary skill to use highly purified EPA and substantially no DHA, these references would have done the opposite, discouraging the use of purified EPA and substantially no DHA.

785. Mori 2000 would have motivated a person of ordinary skill in the art to use DHA, not EPA. As noted above, in March 2008 the most immediate therapeutic goal for patients with very high triglycerides was to lower triglycerides (to address pancreatitis risk), but that lowering cardiovascular risk remained an important therapeutic objective. *See supra* ¶ 111. But, as discussed below, Mori 2000 taught that DHA was *at least as good* as EPA at lowering triglycerides, and potentially *more effective* than EPA at reducing cardiovascular risk. *See infra* ¶¶ 786–88, 794–99. Mori 2000 therefore would have motivated a person of ordinary skill in the art to use DHA, and not EPA.

786. First, Mori 2000 observed a nominally greater reduction in triglycerides with DHA than EPA. *See* DX 1538 at ICOSAPENT_DFNDTS00011028, Mori 2000 at 1087 ("After adjustment for baseline values, fasting triacylglycerols [(triglycerides)] decreased significantly by 18.4% with EPA (P = 0.012) and by 20% with DHA (P = 0.003), relative to the placebo group."). Mori 2000 thus taught that EPA offered no advantage over DHA in terms of triglyceride-lowering, and that, if anything, DHA may be more effective than EPA in reducing triglycerides. A person of ordinary skill reviewing Mori 2000 therefore would not have been motivated to select a composition of purified EPA and substantially no DHA on the basis of triglyceride-lowering considerations.

787. Second, Mori 2000 suggested that, in multiple respects, DHA offered advantages over EPA in terms of potential cardiovascular benefits:

- ***LDL particle size.*** Mori 2000 reported that "[n]either olive oil nor EPA had a significant effect on LDL particle size, whereas DHA supplementation significantly increased LDL particle size (P = 0.002) after adjustment for baseline values (Table 2 and Figure 5)." *Id*. Mori 2000 explained that this increase in LDL particle size "may represent a shift to a less atherogenic LDL particle" and "might be expected to contribute to a reduction in atherogenic risk." *Id*. at ICOSAPENT_DFNDTS00011030–31. As of March 2008, a person of ordinary skill would have understood that smaller LDL particles might be more atherogenic, because they would be more likely to infiltrate the walls of blood vessels, initiating the inflammatory process that can lead to atherosclerosis and cardiovascular disease. Conversely, an agent that increased LDL particle size would reduce atherogenic risk, because large LDL particles would be less likely to infiltrate the walls of blood vessels and arteries. Therefore, as reported in Mori

2000, DHA's increase in LDL particle size "might be expected to contribute to a reduction in atherogenic risk," thereby offering an advantage over EPA. *Id*. at ICOSAPENT_DFNDTS00011031.

- ***HDL cholesterol.*** Mori 2000 reported that "we found that DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL2-cholesterol subfraction." *Id*. at ICOSAPENT_DFNDTS00011029. Mori 2000 further explained that "the increase in HDL2 cholesterol could have a marked effect on the incidence of cardiovascular disease, given that HDL2 cholesterol may be the subfraction of HDL cholesterol that may be the most protective against coronary heart disease." *Id*. at ICOSAPENT_DFNDTS00011031; *see also id.* ("It has been suggested that serum HDL cholesterol is better maintained with DHA-enriched than with EPA-enriched oils. The present data and previous findings support this hypothesis. We observed that the increase in HDL cholesterol was due to a 29% increase in HDL2 cholesterol."). A person of ordinary skill in the art in March 2008 would have understood that, as an agent that increased HDL, DHA possessed another advantage over EPA in terms of reducing cardiovascular risk.

- ***Fasting glucose.*** Diabetes is very common in patients with very high triglycerides. For diabetics, an increase in fasting glucose levels can result in hyperglycemia, which can damage the vessels that supply blood to vital organs, increasing the risk of heart disease and stroke, among other things. An agent that increased fasting glucose therefore would have raised concerns for patients with very high triglycerides, given that many such patients are diabetic. In view of these considerations, Mori 2000 offered another reason to choose DHA over EPA, because Mori 2000 reported that EPA—but not DHA—increased fasting glucose. *Id.* at ICOSAPENT_DFNDTS00011033.

788. Given that Mori 2000 reported that DHA was at least as good as EPA in terms of lowering triglycerides (the primary therapeutic goal for persons with TG levels of at least 500 mg/dl), and offered advantages over EPA in terms of addressing cardiovascular risk (an important second priority for persons with TG levels of at least 500 mg/dl), Mori 2000 would have motivated a person of ordinary skill to select DHA—not EPA—as a triglyceride-lowering agent.

789. That Mori 2000 reported a statistically significant increase in LDL-C of 8% with DHA and a statistically non-significant increase in LDL-C of 3.5% with EPA in persons with mean baseline triglyceride levels of less than 200 mg/dl, *id.* at ICOSAPENT_DFNDTS00011028, does not alter this conclusion. Mori 2000 did not study the

LDL-C effects of highly purified EPA in persons with triglyceride levels of at least 500 mg/dl, and a person of ordinary skill would have expected that both EPA and DHA would dramatically increase LDL-C in that population. *See supra* ¶¶ 115–16. Even in patients with lower baseline triglyceride levels, moreover, a person of ordinary skill would have understood that both DHA and EPA increased LDL-C levels, as revealed by the 2006 review publication by von Schacky discussed above. *See supra* ¶ 742–43. Moreover, a person of ordinary skill would have observed that in Mori 2000, the EPA group had a more than 10 percent lower mean baseline TG level than the DHA group, which could explain the numeric difference in LDL-C results between the groups. *See supra* ¶¶ 682–83. That EPA showed a numerical rise in LDL-C in a group with mean baseline TG levels of 178 mg/dl in Mori 2000 would have provided no assurance that LDL-C would not substantially increase in patients with triglyceride levels of at least 500 mg/dl, who were not even studied in Mori 2000.[17]

790. The other references in Defendants' obviousness combination—Hayashi and Kurabayashi—would not have motivated a person of ordinary skill to substitute highly purified EPA for the composition in LOVAZA® either. Neither of these references taught that one could avoid substantial increases in LDL-C in persons with very high triglycerides by administering highly purified EPA, or provided a reasonable expectation of success in doing so. Indeed, neither of these publications studied lipid effects of purified EPA in populations with very high triglycerides, and Kurabayashi did not look at the effect of EPA alone in any population, but instead studied the effects of EPA in conjunction with estriol.

791. Furthermore, to the extent Kurabayashi suggested anything about EPA, it was that EPA is not a particularly effective triglyceride-lowering agent. In Kurabayashi, almost half the

[17] The experience with TRICOR® illustrates that the absence of a statistically significant increase in LDL-C in persons with TG levels below 500 mg/dl would in no way provide a reasonable expectation of avoiding a large increase in LDL-C in persons with very high triglycerides. With TRICOR®, persons with baseline TG levels (mean of 231 mg/dl) comparable to the baseline TG levels in Mori 2000 (mean baseline TG of 178 mg/dl) experienced a *reduction* in LDL-C levels. *See supra* ¶ 115. Yet persons with very high triglycerides receiving TRICOR® experienced a large statistically significant increase in LDL-C. *See id.*

subjects in the EPA/estriol group did not show improvement in triglyceride levels. *See* PX 376 at 000003, Kurabayashi at ICOSAPENT_DFNDTS00006239 (reporting that only 55% (11 of 20) in the EPA/estradiol group showed improvement in triglyceride levels). Finally, because these publications did not compare purified EPA to DHA, they did not teach that purified EPA offered advantages over DHA.

C. The prior art as a whole confirms that a POSA would not have been motivated to use highly purified EPA with no DHA in patients with very high TGs, or reasonably expected success in avoiding substantial increases in LDL-C in such patients with highly purified EPA

792. The prior art as a whole, including references not included in Defendants' obviousness combination, confirms that a person of ordinary skill would not have been motivated to use high purity EPA, and would not have reasonably expected that such composition would reduce triglycerides without a substantial increase in LDL-C in persons with very high triglycerides.

793. Just as the Mori 2000 reference taught that DHA had advantages over EPA, so did other prior art. For example, there was other prior art suggesting that DHA was more effective than EPA in lowering triglycerides. *See, e.g.*, DX 967 at 000004, Grimsgaard et al., *Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid in Humans Have Similar Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids*, 66 Am. J. Clinical Nutrition 649 (1997) ("Grimsgaard 1997") at ICOSAPENT_DFNDTS00006139 (reporting in comparison of 3.8 g/day EPA versus 3.6 g/day DHA in people with normal triglyceride levels that the "net decreases in serum triacylglycerols [(triglycerides)] were consistently greater in the DHA group than in the EPA group"); PX 997 at 000001, 000005, 000006, Buckley at AMRN00290275, AMRN00290279, AMRN00290280 (observing that DHA was a "more potent hypotriacylglycerolaemic [(hypotriglyceridemic)] agent," and that "DHA may be more efficacious than EPA in improving the plasma lipid profile" when reporting that "[r]elative to the olive-oil placebo group, only the 22% reduction (P=0.032) in the DHA group remained significant, with a non-significant 15% difference between the EPA and olive-oil group").

794. Prior art also suggested that DHA had advantages over EPA in terms of cardiovascular health in a number of respects:

- ***HDL-C.*** HDL—often called the "good" cholesterol—is involved in the process of removing excess cholesterol from arteries. *See supra* ¶ 103. A number of prior art references reported that DHA—and not EPA—increased HDL-C and HDL particle size, which were viewed as cardioprotective. *See, e.g.*, PX 918 at 000008, Agren at AMRN00289902 ("[T]he HDL to LDL cholesterol ratio was increased only in [the DHA-oil] group."); PX 967 at 000004, Grimsgaard 1997 at ICOSAPENT_DFNDTS00006139 ("In the DHA group, HDL cholesterol increased 0.06 mmol/L ($P < 0.001$), differing significantly from both the EPA and corn oil groups."); PX 561 at 000005, Rambjør at AMRN00290978 ("DHA significantly increased HDL_2 C while decreasing HDL_3 C levels … EPA alone had no such effect in confirmation of our findings here.").

- ***LDL-particle size.*** As Mori 2000 reflects, small, dense LDL particles were associated with increased atherogenic risk. *See* DX 1538 at ICOSAPENT_DFNDTS00011031, Mori 2000 at 1090. Beyond Mori 2000, other prior art recognized that DHA increased LDL-C particle size, which could help lower atherogenic risk. *See, e.g.*, PX 563 at 000001, Woodman 2003b at AMRN01066627 ("LDL particle size increased after supplementation with DHA but not EPA.").

- ***Blood pressure.*** High blood pressure was associated with increased risk of cardiovascular disease, and thus a person of ordinary skill in March 2008 would have understood that an agent that was more effective in lowering blood pressure was desirable. Prior art suggested that DHA was more effective in lowering blood pressure than EPA. *See, e.g.*, PX 565 at 000002, Mori 1999 at AMRN01177186 ("Purified DHA but not EPA reduced ambulatory BP [(blood pressure)] and HR [(heart rate)] in mildly hyperlipidemic men. The results of this study suggest that DHA is the principal ω3 fatty acid in fish and fish oils that is responsible for their BP- and HR-lowering effects in humans."); PX 386 at 000006, McLennan et al., *The cardiovascular protective role of docosahexaenoic acid*, 300 European J. Pharmacology 83 (1996) ("McLennan") at AMRN00621424 ("[T]here was a clear order of blood pressure retardation between the diets (docosahexaenoic acid diet > eicosapentaenoic acid + docosahexaenoic acid diet > eicosapentaenoic acid diet). Thus the presence of docosahexaenoic acid seemed to be most important, with eicosapentaenoic acid providing some effect if present in high enough concentrations.").

- ***Heart rate.*** Like blood pressure, elevated heart rate was associated with increased risk of cardiovascular disease, and thus a person of ordinary skill in the art would have viewed an agent that was more effective in lowering heart rate to be desirable. Prior art suggested that DHA was more effective in lowering heart rate than EPA. *See, e.g.*, PX 565 at 000002, Mori 1999 at AMRN01177186 ("Purified DHA but not EPA reduced ambulatory BP [(blood pressure)] and HR [(heart

rate)] in mildly hyperlipidemic men. The results of this study suggest that DHA is the principal ω3 fatty acid in fish and fish oils that is responsible for their BP- and HR-lowering effects in humans."); PX 1028 at 000003, Grimsgaard 1998 at ICOSAPENT_DFNDTS00009274 ("Compared with that in the control group, heart rate in the DHA group decreased and that in the EPA group increased across all values of baseline heart rate.").

- ***Improved endothelial function.*** The endothelium is a thin membrane that lines the inside of the heart and blood vessels. Endothelial cells release substances that control vascular relaxation and contraction. Endothelial dysfunction is of significance in predicting stroke and heart attacks due to the inability of the arteries to dilate fully, and it precedes the development of atherosclerosis. Therefore, improved endothelial function is associated with reduced risk for cardiovascular disease. Prior art suggested that DHA, but not EPA, improved endothelial function. *See, e.g.*, PX 905 at 000007, von Schacky at AMRN-PEXP-0007472 ("[T]he available evidence indicates that EPA-DHA improve endothelial function in patients with cardiovascular disorders. When compared, DHA, but not EPA, was found to be effective.").

- ***Reduced arrhythmia.*** Heart arrhythmia—or irregular heartbeat—refers to conditions in which the heart beats too quickly, too slowly, or with an irregular pattern. When the heart does not beat properly, it cannot pump blood effectively and may lead to stroke or cardiac arrest. Prior art suggested that DHA reduced heart arrhythmia while EPA did not. *See, e.g.*, PX 920 at 000007, Conquer at AMRN00290332 (DHA's antiarrhythmic effect "may account for the reduction in cardiac arrest and sudden cardiac death in those having a higher DHA status.").

795. Some of these benefits were summarized in a 2006 review article by von Schacky, which included a table reflecting that both EPA and DHA were understood to raise LDL-C and that DHA was understood to offer advantages over EPA in terms of HDL effects, platelet aggregability, blood pressure, heart rate, and endothelial function. *See* PX 905 at 000009, von Schacky at AMRN-PEXP-0007474, Table I.

Table I Effects of purified eicosapentaenoic and docosahexaenoic acid, as observed in human studies, only significant differences were considered for inclusion. Arrows reflect semi-quantitatively the findings from the literature

	EPA	DHA
Triglycerides	↓↓	↓↓
Cholesterol	↔	↔
LDL	↑	↑
HDL	↔?	↑?
platelet aggregability	(↓)	↓
mean platelet volume	↓	↔
blood pressure	↔	↓
heart rate	↓	↓↓
endothelial function	↔	↑
glucose metabolism	↔	↔

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Note: Information sourced from von Schacky and Weber 1985; Nozaki et al 1992; Rambjor et al 1996; Grimsgaard et al 1997, 1998; Mori, Bao, et al 1999; Mori, Burke, et al 2000; Mori, Watts, et al 2000; Woodman et al 2000, 2002, 2003a, 2003b; Park and Harris 2002; Mori and Woodman 2006.

796. These benefits would have further motivated a person of ordinary skill in the art to use *DHA*—not highly purified EPA.

797. The prior art as a whole also confirms that considerations relating to LDL-C would not have motivated a person of ordinary skill in March 2008 to use a composition of high purity EPA and substantially no DHA. There was no prior art that measured the effect of high purity EPA on LDL-C in a population having triglycerides of at least 500 mg/dl, and therefore no

study reporting that high purity EPA would avoid the expected large rise in LDL-C observed in such patients with LOVAZA®. And even if one looked to prior art examining the LDL-C effects of DHA and EPA in persons with triglyceride levels below 500 mg/dl, moreover, a person of ordinary skill would not have concluded that the LDL-C effects of DHA and EPA were appreciably different, as studies examining the individual effects of DHA and EPA in persons with lower triglyceride levels generally reported that EPA and DHA had similar effects on LDL-C. *See, e.g.*, PX 905 at 000009, von Schacky at AMRN-PEXP-0007474, Table I (Table showing that DHA and EPA were understood to have the same effect on LDL-C).

798. To be sure, there was inconsistency in the reported LDL-C outcomes for DHA and EPA in persons with normal to high triglyceride levels. *See, e.g.*, PX 914 at 000003, Nozaki et al., *Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary Hypercholesterolemia*, 62 Int'l J. Vitamin & Nutrition Research 256 (1992) ("Nozaki") at ICOSAPENT_DFNDTS00006590 ("There is still controversy concerning the effects of fish oil on low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol levels."); DX 1532 at ICOSAPENT_DFNDTS00006161, Hayashi at 24 ("Data on the effects of fish oils rich in N-3 fatty acids on plasma low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were contradictory in some cases."); PX 909 at 000008, Geppert et al., *Microalgal Docosahexaenoic Acid Decreases Plasma Triacylglycerol in Normolipidaemic Vegetarians: A Randomised Trial*, 95 British J. Nutrition 779 (2006) at ICOSAPENT_DFNDTS00006133 ("Inconsistent effects of DHA on LDL cholesterol levels were reported in previous studies; some investigators found a LDL cholesterol-raising effect of DHA or no effect on LDL cholesterol levels.").

799. But the inconsistency in reported LDL-C outcomes with DHA and EPA is further reason that it was not known or reasonably expected that DHA but not EPA raised LDL-C. Indeed, far from consistently reporting that DHA raised LDL-C but EPA did not, some prior art suggested that EPA—not DHA—raised LDL-C. *See, e.g.*, PX 561 at 000003–05, Rambjør at AMRN00290976-77, AMRN00290978, Table 3 ("We conclude that EPA appears to be

primarily responsible for TG-lowering (and LDL-C raising) effects of fish oil . . . EPA lowered TG and VLDL C by 16% and increased in LDL cholesterol levels by 6% (both P <0.01)"); PX 1022 at 000006, Westerveld et al., *Effects of Low-Dose EPA-E on Glycemic Control, Lipid Profile, Lipoprotein(a), Platelet Aggregation, Viscosity, and Platelet and Vessel Wall Interaction in NIDDM*, 16 Diabetes Care 683 (1993) at AMRN-PEXP-0008420 ("In the 1800-mg group LDL cholesterol increased during EPA-E supplementation as found by others."); *see also* PX 918 at 000003, 000007, Agren at AMRN00289898, AMRN00289902, Table 3 ("[A] study comparing oils with different EPA to DHA ratios indicates that only oil rich in DHA can decrease LDL cholesterol . . . . No tendency to increased LDL cholesterol was seen in the DHA-oil group in the present study."); PX 920 at 000001, 000005, Conquer at AMRN00290326, AMRN00290330, Table 4 ("[N]o significant changes were found in the total and LDL-cholesterol levels with DHA supplementation."). A person of ordinary skill in the art viewing the prior art as a whole therefore would not have understood that DHA increased LDL-C while EPA did not.

D. It was not "obvious to try" high purity EPA with substantially no DHA in patients with TGs of at least 500 mg/dl

800. A person of ordinary skill in the art seeking to achieve the goal of lowering TGs without a substantial increase in LDL-C in persons with very high triglycerides would have had numerous potential options to pursue, including trying to develop a new niacin or fibrate product, a combination product (such as a combination of niacin and LOVAZA® in various dosages), or some new type of triglyceride-lowering agent altogether. Even if one had been limited only to DHA and EPA, there was a vast array of choices of percentages of each that one could include in a mixture, as well as an array of possible dosages.

801. Among such choices, a person of ordinary skill in the art would not have found it obvious to administer 4 g/day of highly purified EPA with substantially no DHA, given all of the potential advantages the prior art reported for DHA, as well as the fact that EPA raised potential concerns about fasting glucose levels in diabetics, who make up a large portion of persons with

very high triglycerides. Nor would a person of ordinary skill in the art have seen an LDL-C advantage with using purified EPA. *See supra* ¶¶ 797–99. And even if one had considered using highly purified EPA, it would not have been predictable, and there would have been no reasonable expectation of success, that a patient could avoid a substantial increase in LDL-C. As discussed above, the strong expectation was that omega-3 fatty acids, including both DHA and EPA, would dramatically increase LDL-C in persons with very high triglycerides, and nothing in the prior art taught otherwise. *See supra* ¶¶ 115–16.

802. Furthermore, real world experience shows that it would not have been obvious to try a composition of high purity EPA with substantially no DHA as a triglyceride-lowering agent in persons with TG levels of at least 500 mg/dl. Although purified EPA had been known since at least the early 1990s, as evidenced by the Epadel JPR from 1991, and it had also been known that OMACOR®/LOVAZA® produced large LDL-C increases in patients with very high triglycerides since the 1990s, as evidenced in PX 824, Harris 1997, no one as of March 2008 had developed a method of lowering TGs in the very high TG population using a composition with highly purified EPA and substantially no DHA. In fact, there were no studies directed to studying the effects of EPA in a population consisting only of persons with triglyceride levels of at least 500 mg/dl. That no one had ever even attempted to study high purity EPA in this population speaks to the non-obviousness of the claimed method.

803. Moreover, around the time of the claimed invention, and even in the years following, researchers continued to pursue omega-3 mixtures containing substantial amounts of DHA. For example, scientists pursued the omega-3 fatty acid treatment EPANOVA®, which contained approximately 550 mg EPA and 200 mg DHA in each 1 gram capsule. Trygg Pharma, Inc. similarly attempted to develop an improved omega-3 fatty acid treatment in its drug OMTRYG®. Each 1.2-gram capsule of OMTRYG® contains approximately 465 mg EPA and 375 mg DHA. PX 850 at 000006, OMTRYG® Label ("OMTRYG® Label 2014") at AMRN03130032. In addition, clinical trials on omega-3 formulations that were underway as of 2008 investigated formulations that included substantial amounts of DHA, including the

OMEGA trial (460 mg EPA/380 mg DHA); ALPHA OMEGA (400 mg EPA-DHA); SU.FOL.OM3 (400 mg EPA/200 mg DHA); ORIGIN (465 mg EPA/375 mg DHA); R&P (500 mg EPA/500 mg DHA); DO-IT (1150 mg EPA/800 mg DHA); ASCEND (460 mg EPA/380 mg DHA). *See infra* ¶¶ 944–56.

E. The prior art would not have motivated a person of ordinary skill to use a 4 g dose

804. A person of ordinary skill in the art would not have been motivated to use high purity EPA with a reasonable expectation of success, and therefore would not have considered the appropriate dose for such a composition. Furthermore, there was no teaching in the art motivating a person of ordinary skill to use 4 g of purified EPA. Mori 2000 reported a smaller triglyceride reduction with 4 g of EPA than Hayashi reported using 1.8 g EPA. *See* DX 1538 at ICOSAPENT_DFNDTS00011028, Mori 2000 at 1087 (reporting 18 percent reduction in TGs with 4 g); DX 1532 at ICOSAPENT_DFNDTS00006163, Hayashi at 26, Table I (reporting 41% percent reduction in TGs with 1.8 g/day dose). And the WO '118 reference that Defendants cite as background prior art stated that the most preferred dose for high purity EPA was 1.8 to 2.7 g/day. *See* DX 1524 at ISOCAPENT_DFNDTS00007082, WO '118 at 22 ("The daily dose in terms of EPA-E is typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day."). The prior art therefore would not have motivated a person of ordinary skill in the art to use a dose of 4 g daily of high purity EPA if one had pursued high purity EPA.

805. Moreover, in 2008, there was a concern that higher doses might interfere with potential cardiovascular benefits from omega-3 fatty acid preparations or even have overall adverse effects. *See, e.g.*, PX 567 at 000005, Nilsen, et al., *Effects of a High-Dose Concentrate of N-3 Fatty Acids or Corn Oil Introduced Early After an Acute Myocardial Infarction on Serum Triacylglycerol and HDL Cholesterol*, 74 Am. J. Clinical Nutrition 50, 54 (2001) at AMRN012134522 ("It is also possible that the high doses [4 g/day] of concentrated n-3 fatty acids applied in this study exceeded some optimal threshold level, outweighing the beneficial effect or even leading to an apparent adverse effect.").

806. The concern that higher doses could interfere with potential cardiovascular benefits or even have adverse effects is evident, for example, from numerous clinical trials that were underway as of 2008 that used daily doses that were considerably lower than 4 g. *See, e.g.*, OMEGA trial (1 g/day); ASCEND (1 g/day); ORIGIN (1 g/day); R&P (1 g/day); ALPHA OMEGA (400 mg); SU.FOL.OM3 (600 mg); DOIT (2.4 g/day); AREDS2 (1 g/day). *See infra* ¶¶ 944–56. The doses selected in these trials reflects the belief as of March 2008 that higher doses would not offer cardiovascular benefits, and may in fact interfere with them—confirming that, as of March 2008, use of a higher daily dose such as 4 g would not have been obvious.

F. Objective indicia further confirm the non-obviousness of the claim

807. Objective indicia of non-obviousness support the Asserted Claims, including that VASCEPA®, and the Asserted Claims whose use VASCEPA® embodies, satisfied long-felt but unmet needs following the failure of others, demonstrated unexpected benefits, received industry praise following initial skepticism, and is a commercial success. *See infra* Section XXXV.

808. Accordingly, Claim 1 of the '728 Patent would not have been obvious to a person of ordinary skill in March 2008.

XXVI. CLAIM 16 OF THE '728 PATENT WAS NOT OBVIOUS

809. Claim 16 of the '728 Patent incorporates the elements of Claim 1 of the '728 Patent, but requires that the pharmaceutical composition comprises no fatty acid, other than ethyl-EPA, in a quantity that is more than 0.6% by weight of all fatty acids combined. By contrast, Claim 1 of the '728 Patent requires that the pharmaceutical composition comprise at least about 96% by weight of all fatty acids present EPA , and substantially no DHA or its esters—*i.e.*, no more than about 4% DHA or its esters. Claim 16 thus requires even less DHA than Claim 1.

810. Defendants challenge Claim 16 of the '728 Patent over the same references as Claim 1 of the '728 Patent—LOVAZA® PDR, Mori 2000, Kurabayashi, and Hayashi—but further in combination with WO '900. Defendants contend that a person of ordinary skill would have been motivated, with a reasonable expectation of success, to use EPA of the high purity

required by Claim 16 for the reasons discussed in conjunction with Claim 1 of the '728 Patent. *See supra* ¶¶ 762–64. Defendants further contend that the additional limitation specifying that the composition comprise no fatty acid other than EPA in a quantity that is more than about 0.6% by weight of all fatty acids combined is also disclosed in WO '900.

811. Claim 16 of the '728 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* ¶¶ 764–808. Those reasons include that (1) the references in Defendants' obviousness combination would not have altered the strong expectation that highly purified EPA would produce large (and statistically significant) LDL-C increases in individuals with severely elevated triglyceride levels, and therefore would not have provided a reasonable expectation that one could reduce triglycerides without substantially and significantly increasing LDL-C in persons with triglyceride levels of at least 500 mg/dl; (2) the references in Defendants obviousness combination would not have motivated a person of ordinary skill to use highly purified EPA and substantially no DHA, as the references in his combination teach that *DHA* had advantages over EPA in terms of cardiovascular benefits; (3) the prior art as a whole confirms that a person of ordinary skill would not have been motivated to use highly purified EPA and substantially no DHA in patients with very high TG levels, given that the prior art as a whole taught that DHA had advantages over EPA, and that EPA would not have offered an LDL-C advantage over DHA; (4) it would not have been obvious to try highly purified EPA with substantially no DHA as a method of lowering triglycerides in persons with very high TG levels without adversely affecting LDL-C levels; (5) the prior art would not have motivated a person of ordinary skill to use a 4 g dose of high purity EPA; and (6) objective indicia further confirm the non-obviousness of the claim.

812. In addition, nothing in the LOVAZA® PDR, Mori 2000, Hayashi, or Kurabayashi even discloses the composition required by Claim 16 of the '728 Patent. Mori 2000 disclosed the use of purified preparations of EPA ethyl ester (approximately 96%) but did not specify that no other fatty acid comprises more than about 0.6% by weight of all fatty acids combined. *See* DX 1538 at ICOSAPENT_DFNDTS0011027, Mori 2000 at 1086. Similarly, Kurabayashi's

Epadel capsules contained over 96.5% EPA and 0.2% vitamin E, but Kurabayashi did not specify that no other fatty acid in the formulation comprises more than 0.06% by weight of all fatty acids combined. *See* PX 376 at 000002, Kurabayashi at ICOSAPENT_DFNDTS00006238. Hayashi did not disclose the purity of EPA, and LOVAZA® disclosed a formulation in which DHA far exceeded 0.6% by weight of all fatty acids combined. *See* DX 1535 at ISOCAPENT_DFNDTS00006711, LOVAZA® PDR at 2699.

813. Tacitly recognizing that these other references do not satisfy the "no more than 0.6% by weight of all fatty acids combined" limitation, Defendants add WO '900 to their obviousness combination. But WO '900 does not bolster Defendants' argument. A person of ordinary skill seeking to make an improved treatment for hypertriglyceridemia would not have looked to WO '900, because that person would have understood that WO '900 did not provide useful or credible clinical guidance about use of EPA, and further understood that WO '900 provided *no* guidance about treating persons with very high triglycerides. *See supra* ¶¶ 711–17.

814. As noted above, the focus of WO '900 is on how to produce EPA-rich compositions. The application is entitled, "Production of Ultrapure EPA and Polar Lipids from Largely Heterotrophic Culture," and descriptions throughout the application make clear that WO '900 is directed to a method of producing EPA:

> In a first broad aspect the invention provides a process for obtaining an eicosapaentaenoic acid (EPA)-rich composition for therapeutic or prophylactic use, wherein the process employs a culture of micro-organisms of a type selected for a capability of largely heretetrophic growth, and a capability of production of EPA, and a capability of photosynthetic lipid production; the process including a culture phase in which cells are grown under conditions in which organic carbon is used as an energy source; the conditions including use of controlled illumination at a level corresponding to an average photosynthetically active irradiance inside the culture of less than 40 µmol photos m-2 s-1 and including imposition of limitation of nutrients selected from a range including phosphorous and silicon; said procedures being undertaken in order to maximise the amount of recoverable polar lipids including at least one EPA side chain, and a harvesting process that creates a composition rich in EPA.

DX 1525 at ICOSAPENT_DFNDTS00007120, WO '900, ll. 350–59.

815. Numerous other passages in WO '900 make clear that the focus of the application is on *production* of EPA-rich oils. *See*, *e.g.*, *id.* ll. 360–442, 622–904.

816. Beyond WO '900's teachings about how to produce EPA, a person of ordinary skill in the art would not have found WO '900 to provide useful or reliable guidance.

817. As noted above, WO '900 includes a list of potential therapeutic uses of EPA enumerated by WO '900. *See supra* ¶ 711. But that list was so long, varied, and unsupported that it would not have been credible to a person of ordinary skill in the art. WO '900 provided:

> In a further alternative aspect the invention provides for use of a composition, as previously described in this section, in the manufacture of a medicament for treatment of a person affected by certain medical conditions or disorders including but not limited to those selected from diabetes (type I, and type II), glycaemic disorders, diabetes-associated hypertension, cancer, osteoarthritis, autoimmune diseases, rheumatoid arthritis, inflammatory and auto-immune diseases other than arthritis, respiratory diseases, neurological disorders, neurodegenerative disorders (including Huntington's disease, Parkinson's disease, Alzheimer's disease, schizophrenia, major depression, unipolar depression, bipolar depression, obsessive compulsive disorder, borderline personality disorder, postnatal depression, organic brain damage, and traumatic brain injury), renal and urinary tract disorders, cardiovascular disorders, cerebrovascular disorders, degenerative diseases of the eye, psychiatric disorders, reproductive disorders, visceral disorders, muscular disorders, metabolic disorders, prostatic hypertrophy and prostatitis, impotence and male infertility, mastalgia, male pattern baldness, osteoporosis, dermatological disorders, dyslexia and other learning disabilities, cancer cachexia, obesity, ulcerative colitis, Crohn's disease, anorexia nervosa, burns, osteoarthritis, osteoporosis, attention deficit/hyperactivity disorder, and early stages of colorectal cancer, lung and kidney diseases, and disorders associated with abnormal growth and development.

DX 1525 at ICOSAPENT_DFNDT00007924–25, WO '900, ll. 482–96.

818. As of March 2008, a person of ordinary skill would have been highly skeptical that EPA was effective in treating the numerous conditions and diseases listed in WO '900—including impotence, cancer, lung disease, Alzheimer's disease, dyslexia, male pattern baldness,

and osteoporosis to name a few. And WO '900's list of conditions and disorders that EPA could supposedly treat was so long and unsupported that a person of ordinary skill in the art would not have lent credence to it (though if such person had, WO '900 would have led them to focus on developing EPA as a treatment for such deadly disorders as cancer or Alzheimer's disease, rather than severe hypertriglyceridemia, which is not even listed in WO '900). Rather, a person of ordinary skill would have concluded from it that WO '900 was not to be taken seriously to the extent it discussed clinical use of EPA.

819. Other statements in WO '900 would have further reinforced the conclusion that WO '900 did not provide credible or useful guidance on the clinical use of EPA. Elsewhere, for example, WO '900 made the incredible suggestion, unsupported by data, that EPA has therapeutic benefits for seemingly every system and tissue in the body:

> Preferably the products when consumed are capable of promoting brain and mental health, cognition and behaviour. . . . Preferably the products when consumed are capable of eliciting health promoting effects on any of the following non limiting list of body systems and tissues; auditory, appetite, arousal, balance, blood, bone, bowel, cardiovascular, digestive, endocrine, enteric, emotional, gastric, hair, hepatic, immune, lymphatic, kineaesthetic, marrow, memory, metabolic, musculoskeletal, neurotransmitter., nasopharyngeal, pancreatic, musculoskeletal, reproductive, respiratory, ocular, oesophagal, olfactory, palate, pulmonary, proprioceptive, renal, skin, sleep, stomach, sensorimotor, skin, urinogenital, wound healing.

Id. at ll. 523–28.

820. A person of ordinary skill in the art would have been aware of no evidence that EPA had such a wide range of therapeutic effects, and WO '900 provided none. The sweeping, unsupported nature of the statements in the passage above would have confirmed to a person of ordinary skill in the art that the clinical statements about EPA in WO '900 were made without care or concern about evidentiary basis, and that WO '900 was not a reliable guide to the therapeutic use of EPA.

821. Moreover, a person of ordinary skill in the art would have understood that WO '900 did not provide any guidance about hypertriglyceridemia, as WO '900 did not mention hypertriglyceridemia, persons with very high triglycerides, the dose or duration for treating such persons, or why EPA would benefit such persons. Nor did it mention LDL-C, or describe a method for avoiding large LDL-C increases in persons with very high triglycerides. The only studies concerning the therapeutic effects of EPA WO '900 cited were Yokoyama and Peet & Horrobin, *id.* at ll. 125–27, but neither of those references examined the effects of EPA in persons with very high triglycerides. WO '900 therefore did not suggest or provide a reasonable expectation that high purity EPA would lower triglycerides in persons with very high TGs without a substantial increase in LDL-C, and a person of ordinary skill in the art seeking to make an improved treatment for hypertriglyceridemia would not have looked to WO '900.

822. That WO '900 mentioned treating so many disorders with high purity EPA—but nowhere mentioned using high purity EPA to lower triglycerides in persons with severe hypertriglyceridemia—demonstrates that it was not obvious to use high purity EPA to lower triglycerides in persons with severe hypotriglyceridemia.

823. WO '900 would not have provided a person of ordinary skill in the art with motivation to use high purity EPA to lower triglycerides in persons with very high triglycerides, nor provided a reasonable expectation of success in doing so without substantially increasing LDL-C.

824. There is also no discussion or evidence in WO '900 of why DHA would be undesirable in treating hypertriglyceridemia. WO '900 only vaguely and generically stated without evidence that "the desired effects of EPA are limited or even reversed by the co-consumption of undesired molecules; … in particular docosahexaenoic acid (DHA) …." *Id.* ll. 130–33. Especially given the absence of any identified particular concern with use of DHA in the context of treating persons with very high triglycerides, or supporting evidence, a person of ordinary skill in the art would not have been influenced by WO '900's statements about the relative benefits of EPA and DHA. More generally, given that WO '900's statements about the

clinical effects of EPA were not credible, a person of ordinary skill in the art would not have even looked to WO '900 if seeking to make improved omega-3 fatty acid treatment for hypertriglyceridemia.

825. Accordingly, Claim 16 of the '728 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXVII. CLAIM 14 OF THE '715 PATENT WAS NOT OBVIOUS

826. Claim 14 of the '715 patent covers the same general method as Claim 1 of the '728 Patent but specifies that the method is administered to effect a statistically significant reduction in TGs and apoB without effecting a statistically significant increase in LDL-C.

827. Defendants challenge Claim 14 of the '715 Patent over the same references as Claim 1 of the '728 Patent—LOVAZA® PDR, Mori 2000, Kurabayashi, and optionally Hayashi.

828. Claim 14 of the '715 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* ¶¶ 764–808.

829. In addition, it would not have been obvious that administration of 4 g per day of the pharmaceutical composition would effect a statistically significant reduction in apoB. A person of ordinary skill in the art would have based her expectation about the effect of high purity EPA on the experience with LOVAZA®, which did not show a statistically significant reduction in apoB. *See supra* ¶¶ 750–51.

830. Defendants attempt to rely upon Kurabayashi to meet this limitation, but Kurabayashi does not disclose that administration of highly purified EPA produces statistically significant reductions in apoB in any population, let alone in persons with very high triglycerides. *See supra* ¶¶ 704–06.

831. As noted above, Kurabayashi did not study the effect of EPA alone, but instead looked at the effect of a combination of EPA and estriol (a lipid-altering agent) on lipid parameters of Japanese post-menopausal women with triglycerides below 500 mg/dl. *See supra* ¶¶ 704–05. Because Kurabayashi did not study the effect of EPA alone, a person of ordinary skill in the art would not have been able to discern the effect that EPA had on apoB, even in the

population that Kurabayashi studied. Moreover, after 12 weeks of treatment, the difference between the apoB value of the group receiving EPA and estriol (119.4 mg/dl) was not significantly different from the apoB value of the estriol group (121.9 mg/dl). *See* PX 376 at 000005, Kurabayashi at ICOSAPENT_DFNDTS00006241, Table 3. Nor was there any statistical difference between the group receiving EPA and estriol and the group receiving estriol after 24 and 48 weeks of treatment. *See id.*

832. Accordingly, Claim 14 of the '715 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXVIII. CLAIM 1 OF THE '677 PATENT WAS NOT OBVIOUS

833. Claim 1 of the '677 Patent is similar to Claim 1 of the '728 Patent. Like Claim 1 of the '728 Patent, Claim 1 of the '677 Patent covers a method of administering high purity EPA (at least 96% by weight of all fatty acids present) to effect a reduction in triglycerides in a subject with very high triglycerides without substantially increasing LDL-C.

834. Defendants challenge Claim 1 of the '677 Patent over the same references as Claim 1 of the '728 Patent—LOVAZA® PDR and Mori 2000, and optionally further in combination with Hayashi and Kurabayashi.

835. Claim 1 of the '677 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* ¶¶ 764–808.

836. The language of Claim 1 of the '677 Patent differs from Claim 1 of the '728 Patent in a couple of respects, but neither of these materially affects the obviousness analysis.

837. First, in contrast to Claim 1 of the '728 Patent, Claim 1 of the '677 Patent is silent on whether the subject receiving the pharmaceutical composition receives a concurrent lipid altering therapy. Claim 1 of the '677 Patent would not have been obvious to a person of ordinary skill in the art in March 2008 regardless of whether the subject was on concurrent lipid altering therapy.

838. And second, the lipid effects in Claim 1 of the '677 Patent are compared to placebo control, whereas the lipid effects in Claim 1 of the '728 Patent are compared to a second

subject who has not received the pharmaceutical composition. It would not have been obvious that the claimed method of high purity EPA would lower triglycerides in a subject with very high triglycerides without substantially increasing LDL-C, whether by comparison to a placebo control or a second subject not receiving the pharmaceutical composition.

839. Accordingly, Claim 1 of the '677 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXIX. CLAIM 8 OF THE '677 PATENT WAS NOT OBVIOUS

840. Claim 8 of the '677 Patent incorporates the elements of Claim 1 of the '677 Patent, but adds the limitation that the method of claim 1 effects "a reduction in apolipoprotein B compared to placebo control."

841. Defendants challenge Claim 8 of the '677 Patent over the same references as Claim 1 of the '677 Patent—LOVAZA® PDR and Mori 2000, and optionally in further combination with Hayashi and Kurabayashi.

842. Claim 8 of the '677 Patent was not obvious for the same reasons that Claim 1 of the '677 Patent was not obvious. *See supra* ¶¶ 833–39. In addition, for the same reasons as discussed above in connection with Claim 14 of the '715 Patent, it was not obvious to administer 4 g of high purity EPA (at least 96% by weight of all fatty acids present) and substantially no DHA to reduce apoB. *See supra* ¶¶ 829–31.

843. The language of Claim 8 of the '677 Patent differs from Claim 14 of the '715 Patent, but this does not materially affect the obviousness analysis. Claim 8 of the '677 Patent specifies that the reduction in apoB be in comparison to a placebo control rather than a second subject. It would not have been obvious that the claimed method of high purity EPA would lower apoB in a subject with very high triglycerides, whether by comparison to a placebo control or a second subject.

844. Accordingly, Claim 8 of the '677 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXX. CLAIM 1 OF THE '652 PATENT WAS NOT OBVIOUS

845. Claim 1 of the '652 Patent is similar to Claim 1 of the '728 Patent. Like Claim 1 of the '728 Patent, Claim 1 of the '652 Patent covers a method of administering high purity EPA to effect a reduction in triglycerides in a subject with very high triglycerides without substantially increasing LDL-C.

846. Defendants challenge Claim 1 of the '652 Patent over the same references as Claim 1 of the '728 Patent—LOVAZA® PDR and Mori 2000, and optionally further in combination with Hayashi and Kurabayashi.

847. Claim 1 of the '652 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* ¶¶ 764–808.

848. The language of Claim 1 of the '652 Patent differs from Claim 1 of the '728 Patent in a couple of respects, but neither materially affects the obviousness analysis.

849. First, in contrast to Claim 1 of the '728 Patent, Claim 1 of the '652 Patent is silent on whether the subject receiving the pharmaceutical composition receives a concurrent lipid altering therapy. Claim 1 of the '652 Patent would not have been obvious to a person of ordinary skill in the art in March 2008 regardless of whether the subject was on concurrent lipid altering therapy.

850. And second, the lipid effects in Claim 1 of the '652 Patent are compared to baseline, whereas the lipid effects in Claim 1 of the '728 Patent are compared to a second subject who has not received the pharmaceutical composition. This does not affect the obviousness analysis because it would not have been obvious that the claimed method of admistering high purity EPA would lower triglycerides in a subject with very high triglycerides without substantially increasing LDL-C, whether by comparison to baseline or a second subject not receiving the pharmaceutical composition.

851. Accordingly, Claim 1 of the '652 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXXI. CLAIM 4 OF THE '560 PATENT WAS NOT OBVIOUS

852. Claim 4 of the '560 patent is similar to Claim 1 of the '728 Patent. Claim 4 of the '560 Patent covers a method of reducing triglycerides in a subject having a fasting baseline TG level of 500 mg/dl to about 1500 mg/dl using high purity EPA. Claim 4 of the '560 Patent adds the limitation that the method effects "a reductions in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5%."

853. Defendants argue that this claim would have been obvious over two distinct combinations of references.

854. ***First Combination***. Defendants challenge Claim 4 of the '560 Patent over the same references as Claim 1 of the '728 Patent—LOVAZA® PDR and Mori 2000, and optionally further in combination with Hayashi and Kurabayashi. Defendants contend that the additional limitation that the method reduces triglycerides by about 10% without increasing LDL-C by more than 5% is disclosed in Mori 2000, Hayashi, and Kurabayashi.

855. Claim 4 of the '560 Patent was not obvious for the same reasons that Claim 1 of the '728 patent was not obvious. *See supra* ¶¶ 764–808.

856. In addition, Mori 2000, Hayashi, and Kurabayashi do not disclose the additional limitation of Claim 4 of the '560 Patent that the method reduce triglycerides by at least 10% without increasing LDL-C by more than 5% in a subject with very high triglycerides. As discussed above in connection with Claim 1 of the '728 Patent, none of these references is directed to, or describes, LDL-C effects in persons with triglycerides of at least 500 mg/dl. *See supra* ¶¶ 770–83. Therefore, they do not disclose a method that does not increase LDL-C by more than 5% in such persons. Moreover, as discussed above, a person of ordinary skill would have expected that administering high purity EPA would dramatically increase LDL-C in persons with very high triglycerides, well in excess of a mere 5%. *See supra* ¶¶ 765–68.

857. There are some differences between Claim 4 of the '560 Patent and Claim 1 of the '728 Patent:

- The high purity EPA composition of Claim 4 of the '560 Patent cannot contain more than 3% DHA, whereas the composition of Claim 1 of the '728 Patent has "substantially no DHA"—*i.e.*, no more than 4% DHA—and at least 96% EPA of all fatty acids present; and

- Claim 4 of the '560 patent requires administering 4 capsules, each capsule comprising about 900 mg to about 1 g, whereas Claim 1 of the '728 Patent specifies a daily dose of about 4 g.

858. These differences are not material to the obviousness analysis. That Claim 4 of the '560 Patent requires that the composition include even less DHA than Claim 1 of the '728 Patent (no more than 3% vs. no more than 4% DHA) does not change that conclusion that the claim would not have been obvious, given, among other things, that a person of ordinary skill in the art would have understood that DHA provided several cardiovascular advantages, and therefore would have wanted to include DHA in *large amounts*. Thus, just as a person of ordinary skill would have wanted to pursue a composition with DHA far in excess of 4%, so too that person would have wanted to pursue a composition containing DHA far in excess of 3%.

859. In addition, the fact that Claim 4 of the '560 Patent requires that the composition be administered in 4 capsules per day, each capsule comprising about 900 mg to about 1 g of EPA, as opposed to 4 g per day of high purity EPA, is not material to the obviousness analysis either, as a 3.6–4 g/day dosage given in 4 capsules would not have been obvious for the same reasons that a 4 g/day dose of high purity EPA would not have been obvious. *See supra* ¶¶ 804–06.

860. ***Second Combination***. Defendants contend that a second, alternative combination of references would have rendered Claim 4 of the '560 Patent obvious. Defendants contend that Claim 4 of the '560 Patent would have been obvious over Epadel PI 2007 in combination with LOVAZA PDR and Hayashi, optionally further in combination with Mori 2000 and WO '900. Defendants will likely argue that the Epadel PI 2007 disclosed that purified EPA was useful in treating hypertriglyceridemia at a dosage of 2.7 g/day, and that there was a desire to modify the treatment disclosed in Epadel PI 2007 to include treatment of severely hypertriglyceridemic patients. Defendants may further argue that the mixture of EPA and DHA was known to treat

patients with triglycerides above 500 mg/dl at a dosage of 4 g/day, and that a person of ordinary skill in the art would have been motivated to use the same dosing for pure EPA because Mori 2000 taught that 4 g pure EPA was effective at reducing triglycerides, and because a person of ordinary skill would have expected that pure EPA would reduce triglycerides in persons with very high triglycerides. Finally, Defendants contend that, at a minimum, using purified EPA to treat patients with triglycerides of at least 500 mg/dl would have been obvious to try.

861. As an initial matter, a person of ordinary skill in the art would not have been motivated to use purified EPA of at least 96% and substantially no DHA in patients with triglyceride levels of at least 500 mg/dl. To the contrary, the prior art would have motivated a person of ordinary skill to use substantial amounts of DHA.

862. As discussed above in connection with other of the Asserted Claims, including Claim 1 of the '728 Patent, a person of ordinary skill in the art in March 2008 would have understood in view of Mori 2000 and other prior art that DHA offered a number of cardiovascular benefits over EPA that a person of ordinary skill in the art would not have wanted to forego. *See supra* ¶¶ 785–88, 791–99. Moreover, that person would not have believed that purified EPA would provide an advantage over DHA in terms of LDL-C effects: a person of ordinary skill in March 2008 would have expected that both DHA and EPA would produce large increases in LDL-C in persons with very high triglycerides, and the prior art as a whole suggested that EPA and DHA had similar LDL-C effects.[18] *See supra* ¶¶ 115–16, 765–67, 797–99. A person of ordinary skill would have been aware that EPA had been reported to increase fasting glucose levels, raising concerns for patients with very high triglycerides, as a large

[18] Defendants suggest that 4 g of purified EPA would have the same TG-lowering effects as LOVAZA® in persons with very high triglycerides, and that DHA, but not EPA, would substantially increase LDL-C in those patients. These positions are fundamentally inconsistent. It was understood as of March 2008 that an increase in LDL-C was a consequence of lowering triglycerides in persons with very high triglycerides. *See, e.g.*, PX 923 at 000005, McKenney 2007 II at AMRN00290743. Therefore, a person of ordinary skill would have understood that purified EPA would increase LDL-C substantially by virtue of lowering TGs in persons with triglycerides of at least 500 mg/dl.

portion of people with severely elevated triglycerides have diabetes. *See supra* ¶ 787 . Thus, far from motivating a person of ordinary skill in the art to use purified EPA and substantially no DHA, the prior art—including the Mori 2000 reference on which Defendants rely—would have motivated a person to use substantial amounts of DHA.

863. In addition, it would not have been "obvious to try" high purity EPA with substantially no DHA in patients with triglyceride levels of at least 500 mg/dl. A person of ordinary skill seeking to develop an improved method of lowering triglycerides in persons with TG levels of at least 500 mg/dl would have had numerous potential options to pursue as of March 2008—including trying to develop a new niacin or fibrate product, a combination product (such as a combination of niacin and LOVAZA® in various dosages), or some new type of TG-lowering agent altogether. Even if one had been limited only to DHA and EPA, there was a vast array of choices of percentages of each that one could include in a mixture, as well as an array of possible dosages. Among such choices, a person of ordinary skill in the art would not have been motivated to administer 4 g/day of highly purified EPA with substantially no DHA for the reasons discussed above.

864. Furthermore, real world experience demonstrates that it would not have been obvious to try a composition of high purity EPA with substantially no DHA as a triglyceride-lowering agent in persons with triglyceride levels of at least 500 mg/dl. Although purified EPA had been known since at least the early 1990s, and it had also been known that OMACOR®/LOVAZA® produced large LDL-C increases in patients with very high triglycerides since the 1990s, no one as of March 2008 had developed a method of lowering triglycerides in the very high TG population using a composition with highly purified EPA and substantially no DHA. *See supra* ¶¶ 802–03. To the contrary, around the time of the claimed invention, and even in the years following, researchers continued to pursue omega-3 mixtures containing substantial amounts of DHA. *See supra* ¶ 803.

865. Moreover, a person of ordinary skill would not have been motivated to use a 4 g dose of high purity EPA based on the references in Defendants' combination, as well as other

prior art. Mori 2000 reported a smaller triglyceride reduction with 4 g of EPA than Hayashi reported using 1.8 g of EPA. *See supra* ¶ 804–06. The Epadel prescribing information indicated an upper limit of 2.7 g of EPA when an excess of triglycerides are presented. DX 1528 at ICOSAPTENT_DFNDTS00008962, Epadel PI 2007. And the WO '118 reference that Defendants cite as background prior art stated that the most preferred dose for high purity EPA is 1.8 to 2.7 g/day. *See* DX 1524 at ISOCAPENT_DFNDTS00007082, WO '118 at 22 ("The daily dose in terms of EPA-E is typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day."). The prior art therefore would not have motivated a person of ordinary skill in the art to use a dose of 4 g daily of high purity EPA if one had pursued high purity EPA.

866. The addition of WO '900 to the obviousness combination does not bolster Defendants' argument. For the reasons discussed in connection to Claim 16 of the '728 Patent, a person of ordinary skill seeking to make an improved treatment for hypertriglyceridemia would not have looked to WO '900, because that person would have understood that WO '900 did not provide useful or credible clinical guidance about use of EPA, and further understood that WO '900 provided *no* guidance about treating persons with very high triglycerides. *See supra* ¶¶ 814–24.

867. Finally, objective indicia of non-obviousness support that Claim 4 of the '560 Patent would not have been obvious over Defendants' second, and alternative, combination. These objective considerations include the fact that VASCEPA®, and the Asserted Claims that embody its use, satisfied long-felt but unmet needs following the failure of others, demonstrated a number of unexpected benefits, received industry praise following initial skepticism, and is a commercial success. *See infra* Section XXXV.

868. Accordingly, Claim 4 of the '560 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXXII. CLAIM 17 OF THE '560 PATENT WAS NOT OBVIOUS

869. Claim 17 of the '560 Patent covers the same method as claim 4 of the '560 patent except that the TG reduction is compared to placebo control.

870. Defendants challenge Claim 17 of the '560 Patent over similar combinations that Defendants contend would have rendered Claim 4 of the '560 Patent obvious—(1) the LOVAZA® PDR and Mori 2000, and optionally in further combination with Hayashi and Kurabayashi; and (2) the Epadel PI 2007 in combination with the LOVAZA® PDR and Hayashi, optionally further in combination with Mori 2000, Kurabayashi, and WO '900.

871. Claim 17 of the '560 Patent was not obvious for the same reasons that Claim 4 of the '560 Patent was not obvious. *See supra* ¶¶ 854–67 . The addition of "compared to placebo control" does not materially affect the obviousness analysis because it would not have been obvious that the claimed method of high purity EPA would lower triglycerides in a subject with very high triglycerides without increasing LDL-C, whether or not the effects were compared to placebo control.

872. Accordingly, Claim 17 of the '560 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXXIII. CLAIM 1 OF THE '929 PATENT WAS NOT OBVIOUS

873. Claim 1 of the '929 Patent is similar to Claim 1 of the '728 Patent. Claim 1 of the '929 Patent covers a method of administering about 4 g high purity EPA and substantially no DHA (not more than about 4%) to reduce triglycerides. But unlike Claim 1 of the '728 Patent, Claim 1 of the '929 Patent lacks a limitation requiring that the method avoid a substantial increase in LDL-C.

874. Defendants argue that this claim would have been obvious over two distinct combinations of references.

875. ***First Combination***. Defendants contend that Claim 1 of the '929 Patent would have been obvious over the same references that they contend would have rendered Claim 1 of

the '728 Patent obvious—the LOVAZA® PDR and Mori 2000, and optionally in further combination with Hayashi and Kurabayashi.

876. Claim 1 of the '929 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* ¶¶ 764–808.

877. While Claim 1 of the '929 Patent does not include a limitation that the claimed method not substantially increase LDL-C, the expectation that highly purified EPA would produce large LDL-C increases in individuals with severely elevated triglyceride levels remains relevant to the analysis, because the purported motivation that Defendants offer as a reason to modify LOVAZA® to use high purity EPA with substantially no DHA is avoiding substantial increases in LDL-C. But because a person of ordinary skill would not have reasonably expected that high purity EPA would reduce triglycerides without substantially increasing LDL-C in persons with triglyceride levels of at least 500 mg/dl, there would have been no such motivation. In addition, a person of ordinary skill in the art would not have wanted to use a method of at least 96% EPA and substantially no DHA, for the additional reason that DHA was understood to have advantages in terms of cardiovascular health that a person of ordinary skill in the art would not have wanted to forego.

878. ***Second Combination***. Defendants contend that Claim 1 of the '929 Patent would have been obvious over a similar alternative combination of references that they contend would have rendered Claim 4 of the '560 Patent obvious—Epadel PI 2007 in combination with the LOVAZA® PDR and Hayashi, optionally further in combination with Mori 2000 and WO '900.

879. Claim 1 of the '929 Patent was not obvious over Defendants' second, and alternative, combination for the same reasons that Claim 4 of the '560 Patent was not obvious. *See supra* ¶¶ 860–67.

880. Finally, objective indicia of non-obviousness support the non-obviousness of Claim 1 of the '929 Patent over Defendants' second, and alternative, combination. These objective considerations include the fact that VASCEPA®, and the Asserted Claims that embody its use, satisfied long-felt but unmet needs following the failure of others, demonstrated a number

of unexpected benefits, received industry praise following initial skepticism, and is a commercial success. *See infra* Section XXXV.

881. Accordingly, Claim 1 of the '929 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXXIV. CLAIM 5 OF THE '929 PATENT WAS NOT OBVIOUS

882. Claim 5 of the '929 Patent incorporates the elements of Claim 1 of the '929 Patent, but further specifies that the claimed method is effective to reduce apoB in subjects who have fasting triglyceride levels of at least 500 mg/dl.

883. As with Claim 1 of the '929 Patent, Defendants advance two proposed combinations of references in opining that these claims would have been obvious.

884. ***First Combination***. As with Claim 1 of the '929 Patent, Defendants contend that claim 5 of the '929 patent would have been obvious over the LOVAZA® PDR and Mori 2000, and optionally in further combination with Hayashi, and Kurabayashi. Claim 5 of the '929 Patent would not have been obvious for the same reasons that Claim 1 of the '929 Patent would not have been obvious. *See supra* ¶¶ 875–77.

885. The additional limitation in Claim 5 of the '929 Patent that the method reduces apoB provides further reason that the claim was not obvious. With respect to the additional limitation in Claim 5 of the '929 Patent that the method reduces apoB, as noted above in connection with Claim 14 of the '715 Patent, a person of ordinary skill in the art would not have even looked to Mori 2000, Hayashi, and Kurabayashi in forming an expectation about the effect of high purity EPA on apoB in persons with very high triglycerides, given that those references are not directed to persons with very high triglycerides. *See supra* ¶¶ 681, 693, 703, 770–83. Moreover, those references did not show the required apoB reductions in any event. *See supra* ¶¶ 685, 700–01, 704–06. A person of ordinary skill would instead have looked to the experience with LOVAZA®—which was the only FDA-approved omega-3 fatty acid for lowering triglycerides in persons with very high triglycerides—which did not show a reduction in apoB in

persons with very high triglycerides. *See supra* ¶¶ 750–51. Nor would a person of ordinary skill have understood that DHA was responsible for increasing apoB.

886. Accordingly, Claim 5 of the '929 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

887. ***Second Combination***. As with Claim 1 of the '929 Patent, Defendants contend that Claim 5 of the '929 Patent would have been obvious over a second, alternative combination—the Epadel PI 2007 in combination with the LOVAZA® PDR and Hayashi, optionally further in combination with one or more of Mori 2000, Kurabayashi, and WO '900.

888. Claim 5 of the '929 Patent would not have been obvious over Defendants' second proposed combination for the same reasons that Claim 1 of the '929 Patent would not have been obvious. *See supra* ¶¶ 878–80.

889. With respect to the additional limitation in Claim 5 of the '929 Patent that the method reduces apoB, as noted above, a person of ordinary skill in the art would not have even looked to Mori 2000, Hayashi, and Kurabayashi in forming an expectation about the effect of high purity EPA on apoB in persons with very high triglycerides, given that those references are not directed to persons with very high triglycerides. *See supra* ¶¶ 681, 693, 703, 770–83.. Moreover, those references did not show the required apoB reductions in any event. *See supra* ¶¶ 685, 700–01, 704–06. A person of ordinary skill would instead have looked to the experience with LOVAZA®—which was the only FDA-approved omega-3 fatty acid for lowering triglycerides in persons with very high triglycerides—which did not show a reduction in apoB in persons with very high triglycerides. *See supra* ¶¶ 750–51.. Nor would a person of ordinary skill have understood that DHA was responsible for increasing apoB.

890. Finally, objective indicia of non-obviousness support that Claim 5 of the '929 Patent would not have been obvious over Defendants' second, and alternative, combination. These objective considerations include the fact that VASCEPA®, and the Asserted Claims that embody its use, satisfied long-felt but unmet needs following the failure of others, demonstrated

a number of unexpected benefits, received industry praise following initial skepticism, and is a commercial success. *See infra* Section XXXV.

891. Accordingly, Claim 5 of the '929 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XXXV. OBJECTIVE INDICIA SUPPORT THE NON-OBVIOUSNESS OF THE ASSERTED CLAIMS

A. VASCEPA® satisfied long-felt but unment needs

892. Evidence that an invention met a long-felt but unsolved need is evidence of non-obviousness. VASCEPA® met a long-felt need in multiple respects. Prior to VASCEPA®, there was a long-felt need for a safe, well-tolerated treatment for very high triglycerides that did not substantially increase LDL-C or otherwise complicate or interfere with long-term cardiovascular outcomes. More generally, there was a long-felt need for an improved TG-lowering product that not only addressed pancreatitis risk but also reduced cardiovascular risk over and above the risk reduction achieved with appropriate statin therapy, including especially in diabetic patients. VASCEPA® met both of these long-felt but previously unsatisfied needs.

1. VASCEPA® met a long-felt need for a safe, well-tolerated medication that lowers TGs in the very high TG population without substantially raising LDL-C.

893. Prior to VASCEPA®, there was a long-felt need for a treatment that lowered TGs in persons with very high TGs, while avoiding substantial increases in LDL-C and serious side effects. As noted above, all approved TG-lowering products for severe hypertriglyceridemia as of 2008 had significant, long-recognized limitations. All caused large increases in LDL-C in persons for very high TGs. *See supra* ¶¶ 127, 134, 137, 143, 148. In addition, niacin had long been known to have serious side effects including flushing, and fibrates raised safety concerns, especially when used with statins. *See supra* ¶¶ 128–32.

894. LDL-C was recognized to be the "most abundant and clearly evident atherogenic lipoprotein," PX 989 000022, ATP-III at AMRN00289936, and to make "the greatest

contribution to the development of atherosclerosis."[19] Consequently, the prior art had long reflected that a "substantial rise in LDL cholesterol" resulting from hypertriglyceridemia treatments was of "*major clinical concern*." PX 1026 at 000007, Carlson at AMRN-PEXP-0008186; *see also* O'Riordan, *MARINE: Ethyl-EPA Reduces Triglyceride Levels Without Raising LDL Cholesterol*, Medscape (Nov. 30, 2010) ("O'Riordan") (noting that "increases in LDL-cholesterol levels are a problematic side effect of therapies that lower triglyceride levels, especially in patients with very high triglyceride levels.").

895. A 1977 study examining the effect of niacin in persons with TG levels exceeding 500 mg/dl observed, for example, that "the finding of *major clinical concern* in this report [was] the sometimes quite substantial rise in LDL cholesterol." PX 1026 at 000007, Carlson at AMRN-PEXP-0008186 (emphasis in original). Concerns about LDL-C increases with fibrates had been reported as early as 1990, and with LOVAZA® (which had earlier been marketed under trade name OMACOR®) no later than 1997. PX 964 at 000002, LOPID® PDR at AMRN-PEXP-0001612; PX 436 at 000001, Harris at AMRN00290443. These LDL-C increases were problematic because they were understood to be atherogenic, and thus ran counter to the secondary but important goal of addressing cardiovascular risk in persons with severe hypertriglyceridemia. LDL-C increases were also understood to be problematic because they interfered with the beneficial effects of statins—by blunting or negating their LDL-C lowering effects—and because they limited the flexibility of doctors to administer the triglyceride-lowering agent as a monotherapy.

896. The longstanding need for a safe TG-lowering product that was both well-tolerated and that avoided substantial increases in LDL-C was evident in prior attempts to develop a product that avoided both of these problems. One such effort involved a proposed formulation combining niacin with OMACOR® (LOVAZA®), as described in a paper by Isley and others. *See* PX 385 at 000001, Isley et al., *Pilot Study of combined therapy with 3-fatty acids*

[19] PX 924 at 000004, McKenney 2005 at AMRN00290755.

and niacin in atherogenic dyslipidemia, 1 Journal of Clinical Lipidology 211 (2007) ("Isley") at AMRN00621043.

897. The Isley paper observed that problematic rises in LDL-C were frequently seen with omega-3 fatty acid treatments, and that "patient acceptance of niacin is limited by a characteristic flushing reaction." *Id.* In an effort to find a product that avoided both of these problems, the authors studied a LOVAZA®-niacin combination to determine whether the combination would result "in favorable changes in triglyceride and HDL-C without an increase in LDL-C, but with decreases in niacin-associated flushing." *Id.* at 000002. The authors believed that such a product might be achieved with a niacin-LOVAZA® combination, because niacin was known to lower LDL-C, while omega-3 fatty acids were believed to "have aspirin-like, antiprostaglandin effects that could theoretically diminish the niacin 'flush.'" *Id.* at 000001–02.

898. While the initial pilot study on this combination offered promising results, the product ultimately failed to come to fruition, as no such product was ever marketed. Yet the proposed combination and rationale for it highlight the longstanding interest in finding a TG-lowering product that would both avoid substantial increases in LDL-C, as well as serious side effects. Other failures speak to the same need, including extended release niacin (which also sought to address the side effect issues of immediate release niacin, but encountered liver toxicity issues). These formulations attempted to harness the TG-lowering effects and avoidance of LDL-C increases associated with immediate release niacin, but at the same time to avoid serious side effects.

899. The need for a safe TG-lowering product that avoids substantial increases in LDL-C while also avoiding serious side effects can be understood in the context of the ATP-III goals. Because the first treatment priority in individuals with severe hypertriglyceridemia was (and still is) avoiding pancreatitis, there was a longstanding need for a medication that not only lowers TGs effectively, but that is also well-tolerated, given that tolerability problems can lead to non-compliance and therefore undermine the efficacy of the regimen. At the same time, because

individuals with very high TG levels are also at risk of cardiovascular disease (and thus have a secondary treatment priority of reducing cardiovascular risk), it was important for the medication to avoid substantial LDL-C increases, as such increases work to the detriment of this second priority. This secondary treatment priority was also why it was important for the medication to avoid interfering with statin therapy, as doing so would interfere with a treatment that reduces cardiovascular risk.

900. Additionally, the fact that VASCEPA® avoids substantial LDL-C increases in persons with very high TGs gives doctors the flexibility to treat such patients in stepwise fashion: to start first with VASCEPA® as a monotherapy to address pancreatitis risk and then, once TGs are lowered below 500 mg/dl, to add a statin (in combination with VASCEPA®) to lower cardiovascular risk. This benefit is explicitly stated in a number of the Asserted Claims, such as Claim 1 of the '728 Patent, which recites a method of lowering TGs "without substantially increasing" LDL-C in a subject "having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy." PX 21 at 000021, U.S. Patent No. 8,293,728 at AMRN-PEXP-000021. Doctors did not have the same flexibility in patients with LOVAZA®, because the large pro-atherogenic increase in LDL-C meant that doctors generally needed to prescribe a statin concurrently with LOVAZA® in an attempt to counteract LOVAZA®'s large increase in LDL-C.

901. In addition, having to combine LOVAZA® with a statin added a pill burden—increasing expense and demands for patient compliance. Moreover, the LDL-C increases associated with LOVAZA® blunted the beneficial LDL-C lowering effects of the statin, running counter to the important secondary treatment goal of minimizing risk of cardiovascular disease in persons with very high triglycerides. Furthermore, statins often could not offset the LDL-C increases caused by LOVAZA® in persons with very high triglycerides, such as instances in

which a patient was statin intolerant,[20] or where the LDL-C increase was too large (median 49.3% compared to placebo) for the statin to offset the increase.[21]

902. VASCEPA® is the first to meet these long-felt needs. As explained above, Amarin demonstrated in the MARINE trial that VASCEPA® reduces TGs in patients with severely elevated TG levels while avoiding serious side effects (including rhabdomyolysis and flushing) and without increasing LDL-C. *See supra* ¶¶ 165–67; *see also* PX 59 at 000006, Weintraub Decl. II ¶¶ 25–27 ("Based on the well-known LDL increase observed in patients with very high triglyceride levels following treatment with fibrates or Lovaza and the well documented side effects observed with niacin and fibrates (both with and without a statin), there has been a long felt but unmet need for a therapy that lowers triglycerides in subjects with very high triglycerides (500 mg/dl – 2000 mg/dl) and that; (a) does not increase LDL, which is associated with atherosclerosis and heart disease; (b) has an improved side effect profile compared to niacin/fibrates."). Moreover, because it avoids a substantial increase in LDL-C in patients with very high triglycerides, and does not present risks of rhabdomyolysis, it does not interfere with

[20] Although statins are generally well-tolerated, a number of patients are intolerant to statins. Common reasons for discontinuation of statin therapy include elevated hepatic enzyme levels, gastrointestinal complaints, and "statin myopathy," which includes myalgia, weakness, cramping, and rhabdomyolysis. *See* PX 972 at 000001, Backes et al., *Effectiveness and Tolerability of Every-Other-Day Rosuvastatin Dosing in Patients with Prior Statin Intolerance,* 42 Annals of Pharmacotherapy 341, 341 (2008) at AMRN-PEXP-0008717 (describing the "common clinical challenge of achieving an aggressive LDL-C goal in a high-risk patient intolerant to statin therapy"); PX 980 at 000004, Oh et al., *Genetic Determinants of Statin Intolerance*, 6 Lipids in Health and Disease 7 (2007) at AMRN-PEXP-0009461 ("There is little doubt that most clinicians who prescribe statin drugs regularly would be aware of these side effects and would consider them to be an important clinical problem that interferes with statin compliance for many.").

[21] Furthermore, the long-felt need was not met by over-the-counter fish oil dietary supplements. These supplements are not appropriate for persons with very high triglycerides, and they do not meet the needs of such persons. Over-the-counter fish oil supplements are classified by FDA as a food product, not as drugs, and raise concerns about, for example, their content and safety, as studies have shown that such supplements do not consistently reflect the composition stated in their labels, and have unacceptably high levels of peroxides. Moreover, patients virtually never consume sufficient quantities of over-the-counter fish oils to be therapeutically meaningful.

or complicate concomitant statin use (and also provides the flexibility to give the treatment as a monotherapy).[22]

903. While this potential increase in LDL-C is concerning for all patients with severe hypertriglyceridemia, it is particularly concerning for diabetic patients. Diabetics are at a significantly increased risk for cardiovascular disease and it is highly undesirable to compound that risk by administering a drug that can dramatically increase LDL-C levels.

904. The introduction of VASCEPA® was an important development in treatment of diabetic patients with severe hypertriglyceridemia. VASCEPA® was the first treatment option available to treat diabetic patients with severe hypertriglyceridemia that was not associated with serious side effects or a significant increase in LDL-C.

2. VASCEPA® met a long-felt need for a TG-lowering agent that significantly lowers cardiovascular risk over and above the risk reduction provided by appropriate statin therapy

905. Beyond a TG-lowering medication that *would not interfere* with ATP-III's secondary goal of reducing cardiovascular risk, there was a further need for a TG-lowering product that would help individuals with severe hypertriglyceridemia *make progress* with such secondary goal at the same time that they addressed the primary risk of pancreatitis. Thus, there was an additional need for a safe, well-tolerated TG-lowering product that would reduce cardiovascular risk, especially beyond the risk reduction provided by statin therapy. And because diabetic patients in particular are at a significantly increased risk of cardiovascular disease, there was a need for a triglyceride lowering medication that also had a positive impact on cardiovascular risk reduction in diabetic patients.

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[22] There was also a more specific need to develop an improved Omega-3 fatty acid TG-lowering treatment for individuals with very high triglycerides. Omega-3 fatty acids avoided the drug-drug interaction and safety concerns posed by fibrates, and also avoided the side effect problems associated with niacin. But, as noted above, the only existing FDA-approved omega-3 fatty acid treatment, LOVAZA®, substantially raised LDL-C in patients with severely elevated TG levels. By providing a safe, effective, well-tolerated omega-3 fatty acid preparation that avoided substantial LDL-C increases in individuals with at least 500 mg/dl, VASCEPA® met a long-felt need in an additional respect.

906. The long-felt need is evidenced by the fact that, over the past several decades, there was a strong effort and desire to find a TG-lowering agent that lowered cardiovascular risk. This was reflected in the numerous clinical trials that were carried out to assess whether various TG-lowering agents could lower cardiovascular risk, especially on top of a statin. For example, efforts to find a fibrate that would lower cardiovascular risk began in the 1970s and 1980s, and continued into the 2000s. *See infra* ¶¶ 907–14. Similar efforts were carried out with niacin-based formulations and various omega-3 fatty acids in the decades leading up to and including the invention. *See infra* ¶¶ 915–56. As the 1990s progressed, and statins became a cornerstone of treatment for reducing cardiovascular risk, this interest in reducing cardiovascular risk focused on finding a TG-lowering agent that would significantly reduce cardiovascular risk beyond the risk reduction provided by statin therapy.[23] These trials are discussed in detail below.

a) Fibrate Trials

907. As of March 2008, the most recently completed trial on the effect of fibrates on cardiovascular disease was the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, whose results were published in 2005. *See* PX 945, Keech et al., *Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events in 9795 People With Type 2 Diabetes Mellitus (the FIELD Study): Randomised Controlled Trial*, 366 Lancet 1849 (2005). But FIELD failed to show a significant cardiovascular benefit with fenofibrate.

908. While the FIELD trial was being completed, another fenofibrate trial—the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial—was also ongoing. *See* PX 943, Ginsberg et al., *Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus*, 362 N. Eng. J. Med. 1563 (2010). The ACCORD trial evaluated the effects of fenofibrate on the risk of

[23] Even in studies where statins were used to lower LDL-C levels below 100 mg/dl, a residual risk for cardiovascular events remains. A residual risk of 65% to 75% has been reported in major statin trials, underscoring the need for a treatment that significantly reduces residual cardiovascular risk. *See* PX 882 at 000021, Kones, *Primary prevention of coronary heart disease: integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey*, 5 Drug Design Development Therapy 325 (2011) at AMRN-PEXP0001559.

cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk of cardiovascular disease, and was designed to address whether use of a fibrate in addition to a statin would reduce the rate of cardiovascular disease compared with a strategy that uses a statin and a placebo. Starting in January 2001, 5,518 subjects with type 2 diabetes who were being treated with open-label simvastatin were assigned to receive either fenofibrate or placebo. *Id.* at 000001–02. At the start of the study, the dose of fenofibrate was 160 mg/day, and the dose was adjusted according to glomerular filtration rate starting in 2004. *Id.* at 000003. Subjects had a median baseline TG level of 162 mg/dl. *Id.* at 000005. The study's primary endpoint was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The results of the trial were published in 2010. After a mean follow-up period of 4.7 years, the combination of fenofibrate and simvastatin did not reduce rates of cardiovascular disease compared with simvastatin and placebo, meaning that fenofibrate failed to show a significant benefit in reducing residual cardiovascular risk. *Id.* at 000003.

909. Following the ACCORD trial, and the failure of the fibrate product TRILIPIX® to demonstrate additional cardiovascular benefit in statin-treated patients in that trial, FDA removed the indication related to statin coadministration from the labeling of TRILIPIX®. *See* PX 947, Withdrawal of Approval of Indications Related to the Coadministration with Statins in Applications for Niacin Extended-Release Tablets and Fenofibric Acid Delayed-Release Capsules, 81 Fed. Reg. 22,612 (Apr. 18, 2016). FDA had initially approved TRILIPIX® on December 15, 2008 for several indications, including for co-administration with a statin based on ostensibly favorable changes in biomarkers, but FDA revoked that indication based on the results of the ACCORD trial.

910. The results from the FIELD trial and ACCORD trials contrasted with results from clinical trials concerning another fibrate, gemfibrozil. Those gemfibrozil trials included the Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT).

911. The Helsinki Heart Study evaluated the effects of 1,200 mg/day of gemfibrozil on primary prevention of coronary heart disease in men 40 to 55 years of age with non-HDL-C levels ≥200 mg/dl. *See* PX 853, Frick et al., *Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men With Dyslipidemia*, 317 N. Eng. J. Med. 1237 (1987). While the results of the study were published in 1987, screening for the study participants started in 1981, with 4,081 subjects being randomly assigned to receive either gemfibrozil or placebo capsules. *Id.* at 000001–02. The subjects were not on statin therapy and had a mean baseline TG level of 176 mg/dl. *Id.* at 000003. The study's primary endpoint was the combined incidence of fatal and nonfatal myocardial infarction and cardiac death. After a mean follow-up period of 60.4 months, there was a 34% reduction in the frequency of cardiac endpoints in the gemfibrozil group compared to the placebo group. *Id.* at 000002, 000004.

912. The VA-HIT study, whose results were published in 1999, evaluated the effects of 1,200 mg/day of gemfibrozil on secondary prevention of coronary heart disease in men under 74 years of age with a history of coronary heart disease, HDL-C levels ≤ 40 mg/dl, LDL-C levels ≤ 140 mg/dL, and TG levels ≤ 300 mg/dl. *See* PX 844, Rubins et al., *Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men With Low Levels of High-Density Lipoprotein Cholesterol,* 341 N. Eng. J. Med. 410 (1999). Starting in September 1991, 2,531 subjects were randomly assigned to receive either gemfibrozil or placebo capsules. The subjects were not on statin therapy and had a mean baseline TG level of 161 mg/dL. *Id*. at 000001, 000003. The study's primary endpoint was the combined incidence of nonfatal myocardial infarction or death from coronary heart disease. After a median follow-up period of 5.1 years, gemfibrozil reduced the risk of nonfatal myocardial infarction or death from coronary heart disease by 22%. *Id*. at 000002–03.

913. But the reductions reported in these studies were not over and above statin treatment, and therefore of less interest by the 2000s. Additionally, given the safety concerns associated with combining gemfibrozil with a statin, gemfibrozil did not provide a safe option for combination therapy.

914. In light of the above, fibrates as a class were not successful in lowering residual cardiovascular risk over and above the risk reduction provided by statins.

a) Niacin Trials

915. As of March 2008, researchers were also investigating whether niacin could provide a well-tolerated medication that would lower cardiovascular risk over and above statin therapy. *See* PX 941, Boden et al., *Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy*, 365 N. Eng. J. Med. 2255 (2011) ("Boden"); PX 944, Landray et al., *Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients*, 371 N. Eng. J. Med. 203 (2014) ("Landray").

916. A trial completed in the 1970s, the Coronary Drug Project, had shown that niacin as a monotherapy significantly reduced nonfatal myocardial infarction and stroke compared with placebo. PX 867, Coronary Drug Project Research Group, *Clofibrate and Niacin in Coronary Heart Disease*, 231 J. Am. Med. Assoc. 360 (1975). But in the study, niacin monotherapy did not significantly lower death due to coronary heart disease or sudden cardiovascular mortality. *See id.* at 000001. And as noted above, niacin had serious side effects, including flushing, that greatly limited its use as a TG-lowering agent. *See supra* ¶¶ 128–32. For these reasons, niacin did not take off as agent to address cardiovascular risk.[24]

917. In the 2000s, researchers began evaluating the incremental effect of niacin on top of statin use. For example, a study called Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 examined the incremental impact of adding niacin to background statin therapy, with the predefined primary endpoint being the change in mean common carotid intima-media thickness (CIMT). PX 895 at 000004, Taylor et al., *Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a*

[24] Other niacin studies prior to the early 2000s suffered from a number of methodological flaws, including that a number of such studies did not use statin monotherapy control groups, and some used high doses of niacin that exceeded the doses that could be used in clinical practice. *See* PX 895 at 000004, Taylor at AMRN-PEXP-0001821.

Double-Blind, Placebo-Controlled Study of Extended-Release Niacin on Atherosclerosis Progression in Secondary Prevention Patients Treated with Statins, 110 Circulation 3512 (2004) ("Taylor") at AMRN-PEXP-0001821. The study also included as one of the secondary endpoints a composite of clinical cardiovascular events including any hospitalization for an acute coronary syndrome (e.g., unstable angina, myocardial infarction), stroke, an arterial revascularization procedure (percutaneous coronary revascularization, coronary bypass surgery, or peripheral vascular revascularization), or sudden cardiac death. *Id.* at 000002.

918. Between 2001 and 2003, 167 patients in ARBITER 2 were enrolled in the study. The patients had known cardiovascular disease, and all of them received statin drugs on entry to the study. 156 of the patients were being treated with simvastatin, and 160 of the patients were receiving a daily dose of ≥ 20 mg. The mean TG level of the patients was 161 mg/dL. The patients were randomized to receive either extended-release niacin or a matching placebo. The niacin medication was initiated at a daily dose of 500 mg for 30 days, and was increased to 1,000 mg for the duration of the 12-month study period. *See id.* at 000002. The results were published in 2004.

919. The ARBITER 2 study publication noted that the treatment of lipid abnormalities was characterized by the primary use of statins to reduce serum levels of LDL-C, but that the protection afforded by these drugs was "incomplete," and that combination therapies that could further reduce cardiovascular risk beyond statin therapy alone were desirable. *Id.* at 3515. But the overall difference in CIMT progression between the niacin and placebo groups was not statistically significant. *See id.* at 000001. Nor was there a statistically significant difference in clinical cardiovascular events in patients treated with niacin (3.8%) compared to placebo (9.6%; p=0.2). *See id.* at 000004–05.

920. Thus, efforts to find a well-tolerated niacin-based medication that reduced cardiovascular risk over and above statin therapy continued and, as of 2008, additional clinical trials were underway in the hope of finding one.

921. One such trial, the AIM-HIGH study, evaluated the effects of 1,500 to 2,000 mg per day of extended-release niacin on the incidence of major cardiac events among patients with coronary heart disease receiving simvastatin therapy. *See* PX 951 at 000001, Boden at AMRN03143149. The trial was designed to test the hypothesis that niacin added to optimal statin therapy will reduce the risk of cardiovascular events compared with statins alone in patients with respect to atherosclerotic cardiovascular disease. The results of AIM-HIGH were published in 2011, but the study was initiated at least as early as 2008, given the 3-year length of the study. *Id.*

922. In the trial, 3,414 subjects were randomly assigned to receive niacin or placebo after 4-to-8-week open-label phase during which they received simvastatin at a dose of 40 mg/day. *Id.* at 000003–04. The subjects had a median TG level of 163 mg/dl. *Id.* at 000008. The study's primary endpoint was the composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. After a mean follow-up period of 3 years, the trial was stopped due to a lack of efficacy. The addition of niacin to simvastatin therapy provided no incremental benefit in reducing cardiovascular events over the 3-year follow-up period. *Id.* at 000001, 000003.

923. Another trial, the HPS2-THRIVE study, evaluated the effects of 2 g of extended-release niacin and 40 mg of laropiprant on the risk of major cardiovascular events in patients with a history of cardiovascular disease receiving simvastatin or simvastatin and ezetimibe. PX 944 at 000001, Landray at AMRN03146265. Like AIM-HIGH, the trial also failed to show a cardiovascular benefit with a niacin formulation.

924. HPS2-THRIVE was designed to assess the effects of adding an extended-release niacin formulation, in combination with the anti-flushing agent laropiprant, to an effective statin-based treatment for high-risk patients with prior vascular disease. *Id.* The proposed combination was to be called CORDAPTIVE®. *See* PX 864, Carey. But Merck, the developer of CORDAPTIVE®, was never able to obtain FDA approval to sell this drug. And in HPS-2

THRIVE, CORDAPTIVE® failed to demonstrate any cardiovascular benefit in high-risk patients compared to placebo. PX 944 at 000001, Landray at AMRN03146265. In addition, the adverse event rate with CORDAPTIVE® was deemed to be unacceptably high. *Id.* at 000001, 000009. In particular, the study called into question the safety of niacin in diabetic patients. The study found serious complications relating to glucose control as a result of the therapy and new diagnoses of diabetes increased by one third. *Id.* at 000009.

925. Following these trials, FDA revoked the indication for statin co-administration from the product label of extended release niacin (*i.e.* NIASPAN®). *See* PX 947 at 000001, Withdrawal of Approval of Indications Related to the Coadministration with Statins in Applications for Niacin Extended-Release Tablets and Fenofibric Acid Delayed-Release Capsules, 81 Fed. Reg. at 22612, AMRN03146455. FDA had previously allowed indications for use of NIASPAN® in combination with lovastatin and simvastatin (*see* PX 873, FDA, Supplemental Approval, NDA 20381/S-051 (Apr. 27, 2015); PX 575, NIASPAN® Label (2015)), but revoked such indication after AIM-HIGH and HPS2-THRIVE failed to show an incremental benefit with extended release niacin over and above statin use. *See* PX 947 at 000001, 81 Fed. Reg. at 22612, AMRN03146455.

b) Omega-3 Trials

926. As of March 2008, a number of clinical trials had investigated whether omega-3 fatty acids may provide cardiovascular benefits, but the benefits remained unclear, and questions about the clinical value of omega-3 fatty acids had been highlighted, for example, by a recent meta-analysis by the Cochrane collaboration, which concluded that long chain omega-3 fatty acids had no clear effect on total mortality, combined cardiovascular events or cancer. *See* PX 848, Hooper et al., *Risks and Benefits of Omega 3 Fats for Mortality, Cardiovascular Disease, and Cancer: Systematic Review*, 332 BMJ 752 (2006).

927. Some clinical trials had reported possible cardio-protective benefits. *See, e.g.*, PX 932, GISSI-Prevenzione Investigators, *Dietary Supplementation With n-3 Polyunsaturated Fatty Acids and Vitamin E After Myocardial Infarction: Results of the GISSI-Prevenzione Trial*, 354

Lancet 447 (1999) ("GISSI-Prevenzione Investigators"); DX 1553, Yokoyama et al., *Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (JELIS): A Randomised Open-Label, Blinded Endpoint Analysis*, 369 Lancet 1090 (2007) ("Yokoyama 2007"). But these trials had significant methodological shortcomings that left their findings in question, as evidenced by the fact that, following these trials, the effects of omega-3 fatty acids continued to be examined to determine whether they have a clinical cardiovascular benefit.

928. ***GISSI.*** Results from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione (GISSI-P) study were published in 1999. *See* PX 932, GISSI-Prevenzione Investigators. The GISSI-P study evaluated the effects of 1 g/day of omega-3 fatty acids, vitamin E, or both on the risk of major cardiovascular events in patients with recent myocardial infarction. 11,324 subjects participated in the study, and their mean baseline TG level was 162 mg/dl. *Id.* at 000001–02. A mere 4.7% of the subjects were on statin therapy at the start of the study,[25] which increased to 46% at study end. The primary combined efficacy endpoint was death, non-fatal myocardial infarction, and stroke. *Id.* at 000003. The four-way analysis showed a relative decrease in risk for the combined endpoint of 15% with n-3 fatty acids after a mean follow-up period of 3.5 years. *Id.* at 000005–06.

929. But GISSI was an open-label trial, meaning that it did not attempt to disguise the drug administered. Open-label studies are subject to bias, because both the study subjects and trial investigators are aware of what treatment is being administered, and such knowledge can influence their behavior, such as whether and to what extent subjects report symptoms—thereby potentially skewing the results and rendering them unreliable. Additionally, GISSI would have provided no expectation that the omega-3 preparation administered would provide significant cardiovascular risk reduction over statin treatment, because the overwhelming majority of subjects did not use a statin at the beginning of the trial, and a majority remained off statin therapy by the end.

[25] Statins were not supported by definitive data on efficacy when the trial began.

930. ***JELIS.*** Another trial, the JELIS study, was an open-label trial that evaluated the effects of 1.8 g/day of EPA in addition to a low-dose statin (10 mg/day pravastatin or 5 mg/day simvastatin) on the risk of major coronary events in hypercholesterolemic patients. *See generally* DX 1553, Yokoyama 2007. 3,664 Japanese subjects with coronary artery disease (for secondary prevention) and 14,981 Japanese subjects without coronary heart disease (for primary prevention) were randomly assigned to receive EPA with statin or statin alone. *Id.* at ICOSAPENT_DFNDTS00007158. The subjects had a median baseline TG level of 153 mg/dL (1.73 mmol/L). *Id.* at ICOSAPENT_DFNDTS00007159. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. After a mean follow-up period of 4.6 years, major coronary events were reported reduced by 19% in the EPA group but the JELIS study was unable to establish a statistically significant reduction in risk of major coronary events in a subanalysis of the Japanese hypercholesterolaemic patient population with diabetes (HR 0.86 CI 0.65–1.15). *Id.* at ICOSAPENT_DFNDTS00007157. More importantly, the JELIS study had numerous methodological flaws, all of which led the FDA to conclude that JELIS was insufficient to show that high purity EPA has a cardiovascular benefit. *See, e.g.*, PX 994 at 000014–15, Declaration of Curtis Rosebraugh, *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, Civil No. 1:15-CV-03588 (S.D.N.Y. June 23, 2015), ECF No. 54 ("Rosebraugh Decl.") ¶¶ 26–27, AMRN-PEXP-0009056–57; PX 986 at 000155, EMDAC Transcript at AMRN00112407 ln.4–14.

931. *Statin Dose.* As with GISSI, JELIS would have provided no expectation that the omega-3 preparation administered would provide significant cardiovascular risk reduction over appropriate statin treatment. In JELIS, baseline LDL-C levels of the study subjects were high. The mean baseline LDL-C level of patients was 182 mg/dl—a level at which "atherogenesis proceeds at a significant rate." DX 1553 at ICOSAPENT_DFNDTS00007159, Yokoyama 2007 at 1092; PX 989 at 000023, ATP-III at AMRN00289937. Average daily statin doses were 5.6 mg of simvastatin, and 10 mg pravastatin. DX 1553 at ICOSAPENT_DFNDTS00007159,

Yokoyama 2007 at 1092. These are very low statin doses, leaving uncertain whether any apparent reduction in residual risk observed in JELIS was the result of under-dosing of the statin. *See, e.g.*, PX 994 at 000014–15, Rosebraugh Decl. ¶ 26, AMRN-PEXP-0009056 ("First, the subjects in the JELIS trial were limited to Japanese adults receiving a low dose of statin therapy that may be considered inadequate in the United States."); PX 986 at 000155, EMDAC Transcript at AMRN00112407 ln.4–14 ("There are several limitations to the JELIS study. . . . Second, a low dose of statins was used. It is unknown if these patients had been optimally treated with statins using contemporary LDL targets in the United States, whether the positive treatment effects would have persisted."). Furthermore, because JELIS was carried out in subjects who were hypercholesterolemic, DX 1553 at ICOSAPENT_DFNDTS00007157–58, Yokoyama 2007 at 1090–91, JELIS was not designed to determine whether EPA could reduce cardiovascular risk in patients whose cholesterol levels had already been well-controlled through use of a statin.

932. *Japanese Population.* Furthermore, JELIS was conducted in an exclusively Japanese population, and the study left unclear whether the results observed may have been attributable to unique aspects of this population, such as differences in diet (*e.g.*, greater fish consumption), greater baseline EPA levels, and triglyceride levels. For this reason, the study paper itself acknowledged that results of JELIS could not be generalized to other populations. *Id.* at ICOSAPENT_DFNDTS00007164.

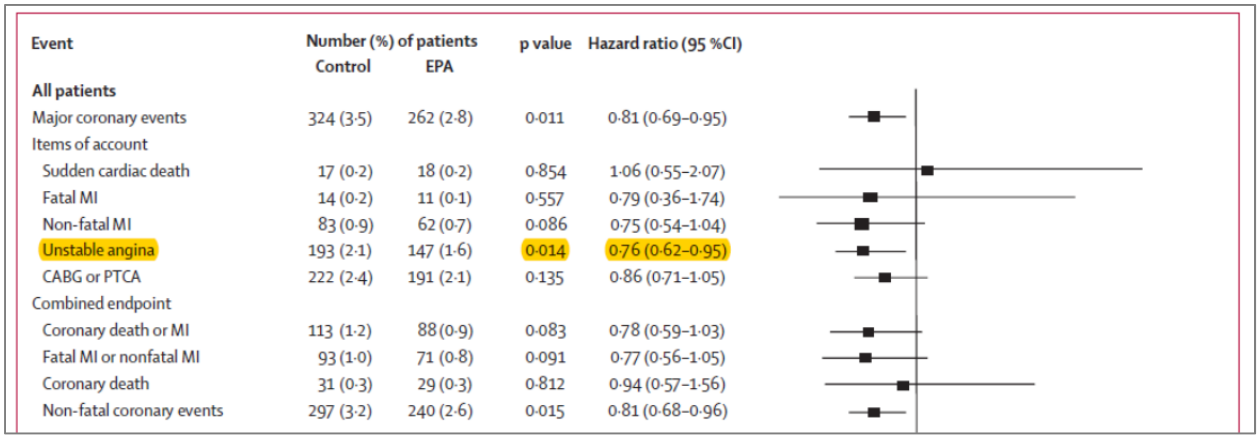
933. *Open Label.* Like GISSI, JELIS was an open-label trial, and therefore subject to bias. Open-label studies are subject to bias, because both the study subjects and trial investigators are aware of what treatment is being administered, and such knowledge can influence their behavior, such as whether and to what extent subjects report symptoms—thereby potentially skewing the results and rendering them unreliable.

934. Empirical evidence suggests that, as a general matter, blinding in trials does indeed make a difference. For example, in a systematic review of 250 randomized controlled clinical trials identified from 33 meta-analyses, researchers observed a significant difference in the size of the estimated treatment effect between trials that reported "double-blinding"

compared with those that did not ($p = 0.01$), with an overall odds ratio 17% larger in studies that did not report blinding. PX 1155, Schulz et al., *Empirical Evidence of Bias: Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled Trials,* 273 JAMA 408 (1995).

935. In JELIS, the study investigators acknowledged that they "[could] not exclude the possibility of bias in some of the physician-initiated endpoints, such as coronary revascularisation and hospital treatment for unstable angina," and this was one reason that FDA believed JELIS was insufficient to conclude that high purity EPA has a cardiovascular benefit. *See* DX 1553 at ICOSAPENT_DFNDTS00007163, Yokoyama at 1096; *see also* PX 994 at 000014, Rosebraugh Decl. ¶ 26, AMRN-PEXP-0009057 ("A subjective endpoint such as unstable angina may be particularly unreliable in an open-label trial where patients and physicians are making decision regarding hospitalizations."); PX 986 at 000155–56, EMDAC Transcript at AMRN00112407 ln.15–AMRN00112408 ln.1 ("JELIS was an open label trial, which could influence patient and physician behavior in reporting of symptoms, decisions regarding hospitalization, and referral of events for adjudication. This may be particularly relevant since hospitalizations for unstable angina was a primary contributor of the overall positive result and is considered a softer endpoint than fatal cardiovascular events.").

936. Moreover, JELIS' positive outcome was driven in large part, if not exclusively, by the outcome on a single parameter—unstable angina—that was subjective and highly susceptible to be skewed by bias from JELIS' open-label design. The primary endpoint in the JELIS trial was "any major coronary event"—defined as sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. DX 1553 at ICOSAPENT_DFNDTS00007158, Yokoyama at 1091. But only one of the components of that primary endpoint—unstable angina—showed a statistically significant reduction in relative risk. This is evident from Figure 3 in the Yokoyama publication:



Event	Number (%) of patients: Control	Number (%) of patients: EPA	p value	Hazard ratio (95 %CI)
All patients				
Major coronary events	324 (3·5)	262 (2·8)	0·011	0·81 (0·69–0·95)
Items of account				
Sudden cardiac death	17 (0·2)	18 (0·2)	0·854	1·06 (0·55–2·07)
Fatal MI	14 (0·2)	11 (0·1)	0·557	0·79 (0·36–1·74)
Non-fatal MI	83 (0·9)	62 (0·7)	0·086	0·75 (0·54–1·04)
Unstable angina	193 (2·1)	147 (1·6)	0·014	0·76 (0·62–0·95)
CABG or PTCA	222 (2·4)	191 (2·1)	0·135	0·86 (0·71–1·05)
Combined endpoint				
Coronary death or MI	113 (1·2)	88 (0·9)	0·083	0·78 (0·59–1·03)
Fatal MI or nonfatal MI	93 (1·0)	71 (0·8)	0·091	0·77 (0·56–1·05)
Coronary death	31 (0·3)	29 (0·3)	0·812	0·94 (0·57–1·56)
Non-fatal coronary events	297 (3·2)	240 (2·6)	0·015	0·81 (0·68–0·96)

Id. at ICOSAPENT_DFNDTS00007161, Figure 3.

937. Figure 3 plots estimated hazard ratios of clinical endpoints stratified by prevention stratum, listing error bars (denoting margins of error) for the hazard ratio of each of the components of the primary endpoint for "Major coronary event." *See id*. Only those error bars that are completely to the left of, and do not cross, 1 favor EPA in a statistically significant way.

938. At the top of the figure, the primary endpoint for "major coronary events" reveals a statistically significant result favoring EPA—*i.e.*, an overall positive outcome for the trial. But when one looks below at the components of that composite outcome, the only component that shows a statistically significant result favoring EPA is unstable angina; the error bar of every other endpoint crosses unity (and has a p-value exceeding 0.05), meaning that none of the other components was statistically different from statin alone. *Id*. Thus, the primary if not exclusive driver for the overall positive outcome in JELIS was unstable angina.

939. That the unstable angina component showed a statistically significant reduction in risk—while no other component of the primary endpoint did—suggests a strong possibility that bias may in fact have influenced the results. That is because, if the EPA preparation truly did reduce cardiovascular risk, one would have expected to see such beneficial effect expressed in showing of statistical significance in a *variety* of different components—not just a single component.

940. That bias may have played a role in skewing the results in the JELIS trial is even more likely given that the one component that did show a statistically significant result—unstable angina—is a relatively subjective endpoint, and thus more susceptible to bias than more objective measures, such as fatal myocardial infarctions. That was particularly the case in JELIS, given the open-label nature of the trial, and that unstable angina can be a challenging diagnosis—easily confused for other conditions that are not related to cardiovascular disease, including heartburn, costochondritis (inflammation of the cartilage connecting the ribs to the sternum), and pulmonary embolism (blood clot in the lungs). Therefore, there is reason to suspect that bias may have influenced the outcome of the JELIS trial—and certainly a person of ordinary skill in the art in 2008 would have so concluded.

941. The possibility of bias from the open-label nature of the JELIS study, coupled with the subjectivity of the unstable angina component, were of concern to FDA when interpreting the JELIS study. As Curtis Rosebraugh, the Director of the Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, FDA explained in a statement made in 2015 about the JELIS trial:

> As part of its presentation to the advisory committee during the October 16, 2013, meeting, as well as when considering whether to rescind the SPA agreement for the ANCHOR trial, FDA reviewed the published results of the JELIS trial. FDA identified limitations to the design of the JELIS trial that affect the interpretation of the trial's results. First, the subjects in the JELIS trial were limited to Japanese adults receiving a low dose of statin therapy that may be considered inadequate in the United States. *Second, the JELIS trial was an open-label trial. In such a trial, both researchers and participants know whether a participant is being administered the drug or placebo. Having this knowledge can influence physician and patient behavior, such as the reporting of symptoms. Third, the main component of the primary endpoint in the JELIS trial was unstable angina, which is a more subjective endpoint than, for example, objective major adverse cardiovascular event endpoints (e.g., heart attack, stroke, or cardiovascular death). A subjective endpoint such as unstable angina may be particularly unreliable in an open-label trial where patients and physicians are making decisions regarding hospitalizations*.

PX 994 at 000014–15, Rosebraugh Decl. ¶ 26, AMRN-PEXP-0009056–57 (emphasis added).

942. The same concern had been articulated by Mary Roberts, M.D., Clinical Reviewer at the Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, FDA at the October 16, 2013 Endocrinologic and Metabolic Drugs Advisory Committee Meeting:

> There are several limitations to the JELIS study. First, the patient population was exclusively Japanese, the majority of the participants were women, and at baseline, patients had a much higher LDL, limiting its generalizability to the intended target population.
>
> Second, a low dose of statin was used. It is unknown if these patients had been optimally treated with statins using contemporary LDL targets in the United States, whether the positive treatment effects would have persisted.
>
> *Third, JELIS was an open label trial, which could influence patient and physician behavior in reporting of symptoms, decisions regarding hospitalization, and referral of events for adjudication. This may be particularly relevant since hospitalizations for unstable angina was a primary contributor of the overall positive result and is considered a softer endpoint than fatal cardiovascular events.*
>
> Finally, in order to approve the indication we are discussing today, we need to be confident that the changes in lipids observed in ANCHOR will translate into cardiovascular benefit. *The relevance of a single open label cardiovascular outcomes trial conducted in Japan that has not been submitted to the division for independent review is questionable.*
>
> In part, the issues just discussed regarding the applicability of the results in the JELIS trial to U.S. population prompted the division to request that a cardiovascular outcomes trial be conducted to provide definitive conclusions regarding the addition of EPA to statins on cardiovascular events.

PX 986 at 000155–56, EMDAC Transcript at AMRN00112407 ln.4–AMRN00112408 ln.16 (emphasis added).

943. Finally, a person of ordinary skill in the art as of March 2008 would not have expected that any potential cardiovascular benefits reported in JELIS or GISSI would be applicable to persons with at least 500 mg/dl. As explained above, as of March 2008, a person of

ordinary skill would have expected that an omega-3 fatty acid preparation, including purified EPA, would dramatically increase LDL-C, a pro-atherogenic lipid that would exacerbate cardiovascular risk rather than reduce it. *See supra* ¶¶ 115–16. There is no indication that the JELIS or GISSI population had TG levels of at least 500 mg/dl; the median baseline TG level in JELIS was 153 mg/dl, and the mean baseline TG level in GISSI was 162 mg/dl.[26] PX 932 at 000002, GISSI-Prevenzione Investigators at AMRN00944985; DX 1553 at ICOSAPENT_DFNDTS00007159, Yokoyama 2007 at 1092.

944. ***Omega-3 Trials Underway as of March 2008.*** That it was not established as of March 2008 that omega-3 fatty acids would provide clinical cardiovascular benefits is clear from the fact that numerous other clinical trials examining the effects of omega-3 fatty acids continued to be undertaken—which would not have been done if the benefits were already established.

945. Ongoing trials as of 2008 included Alpha Omega, DOIT, OMEGA, ORIGIN, SU.FOL.OM3, R&P, AREDS2, and ASCEND, and additional clinical trials that were initiated after 2008 included the VITAL trial. Prior to the REDUCE-IT trial, all of these trials failed to show a significant clinical cardiovascular benefit, causing the existing doubts about omega-3 fatty acids to continue to grow.

[26] This is also true for the results from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Heart Failure (GISSI-HF), published in August 2008. *See* PX 934, GISSI-HF Investigators, *Effect of n-3 Polyunsaturated Fatty Acids in Patients with Chronic Heart Failure (the GISSI-HF Trial): A Randomised, Double-Blind, Placebo-Controlled Trial*, 372 Lancet 1223 (2008). The GISSI-HF study evaluated the effect of 1 g/day of omega-3 fatty acids on mortality and admission to hospital in patients with symptomatic heart failure in subjects with a median TG level of 126 mg/dL (1.42 mmol/L). *Id.* at 000001, 000006. Given the understanding in 2008, a person of ordinary skill would not have expected that any cardiovascular benefits observed in this study be applicable to persons with at least 500 mg/dl. Additionally, only 22% of subjects in the trial were on statin therapy, and therefore the study did not shed light on whether the omega-3 preparation administered would provide significant cardiovascular risk reduction over and above appropriate statin therapy. *Id.* at 000003. Furthermore, all-cause mortality or hospital admission for cardiovascular reasons was reduced by only a modest 8%.

946. The Alpha Omega Trial evaluated the effects of omega-3 fatty acids on the rate of cardiovascular events among patients who have had a myocardial infarction. *See* PX 492, Kromhout et al., *n-3 Fatty Acids and Cardiovascular Events After Myocardial Infarction*, 363 N. Eng. J. Med. 2015 (2010). Patients were enrolled starting April 2002 and randomly assigned to receive one of four trial margarines: a placebo margarine, a margarine containing approximately 400 mg of EPA-DHA per day, a margarine containing 2 g of alpha-linolenic acid (ALA) per day, or a margarine containing combination of EPA-DHA and ALA. *Id.* at 000002. The median TG of the patients receiving EPA-DHA margarines was 144 mg/dL (1.63 mmol/L). *Id.* at 000006. 86% of the patients were on lipid-modifying treatment (mainly statins). The primary endpoint of the trial was major cardiovascular events, which comprised fatal and nonfatal cardiovascular disease and the cardiac interventions percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). *Id.* at 000004. After a median follow-up period of 40.8 months, neither EPA-DHA nor ALA significantly reduced the rate of major cardiovascular events. *Id.*

947. The Diet and Omega-3 Intervention Trial (DOIT), whose results were published in October 2010, evaluated the effects of 2.4 g/day of omega-3 fatty acids on all-cause mortality in men aged ≥ 50 years. 563 participants were randomized into four groups: no dietary counseling and placebo, diet only, omega-3 fatty acids only, and combined dietary counseling and omega-3 fatty acids. *See* PX 938 at 000002–03, Einvik et al., *A Randomized Clinical Trial on n-3 Polyunsaturated Fatty Acids Supplementation and All-Cause Mortality in Elderly Men at High Cardiovascular Risk*, 17 Eur. J. Cardiovascular Prevention & Rehabilitation 588, 588–89 (2010) at AMRN02642568–69. The participants' median TG level was 150 mg/dL (1.7 mmol/L). The primary endpoints in the study were changes in carotid intima-media thickness, circulating biomarkers, and peripheral pulse wave propagation. All-cause mortality and cardiovascular events were reported as nonprimary endpoints. Cardiovascular events were defined as fatal or nonfatal sudden cardiac arrest, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, cerebral stroke, surgery on abdominal aortic aneurysm, or peripheral revascularization procedures. *Id.* at 000004. After 3 years, there was no

statistically significant reduction in all-cause mortality or cardiovascular events. *Id.* at 000002, 000005.

948. The OMEGA trial was a prospective, randomized, double-blind, controlled trial including 3,851 patients that evaluated the effects of 1 g/day of omega-3 fatty acids on the rate of sudden cardiac death. *See* PX 936 at 000001, Rauch et al., *OMEGA, a Randomized, Placebo-Controlled Trial to Test the Effect of Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy After Myocardial Infarction*, 122 Circulation 2152, 2152 (2010) at AMRN01521523. The trial defined the primary endpoint of sudden cardiac death as unexpected death resulting from heart disease occurring within 1 hour of the first symptoms or unwitnessed overnight. *Id.* at 000003. 94% of the patients received statin therapy. *Id.* at 000005. Patients were randomized to receive gelatin capsules containing omega-3 fatty acids or placebo, and the group receiving omega-3 fatty acids had a mean baseline TG of 121 mg/dL (1.37 mmol/L). After a follow-up period of 1 year, the study failed to support a reduction in the rate of sudden cardiac death. *Id.* at 000003, 000007.

949. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial evaluated the effects omega-3 fatty acids on the occurrence of cardiovascular events in diabetic patients with recent myocardial infarction or heart failure. *See* PX 948, Bosch et al., *n-3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia*, 367 N. Eng. J. Med. 309 (2012). The ORIGIN trial was a randomized trial with a 2-by-2 factorial design with a 1 g/day capsule containing at least 900 mg of omega-3 fatty acid ethyl esters. *Id.* at 000001. Randomization of the study's 12,536 participants began in September 2003, and participants received either 1 g/day of omega-3 fatty acids or placebo. *Id.* at 000002, 000005. The participants receiving omega-3 fatty acids had a median TG level of 142 mg/dL, and 53% of them were on statin therapy. *Id.* at 000005. The primary endpoint was death from cardiovascular causes. After a median follow-up period of 6.2 years, daily supplementation with 1 g/day of omega-3 fatty acids did not reduce the rate of cardiovascular events. *Id.* at 000001.

950. The ORIGIN and Legacy Effects (ORIGINALE) study measured posttrial effects of the interventions in the ORIGIN trial for an additional 2.7 years. *See* PX 965, ORIGIN Trial Investigators, *Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (Originale)*, 39 Diabetes Care 709 (2016). This post-trial analysis revealed that during the 6+ years of treatment followed by more than 2.5 years of observation, omega-3 fatty acid supplementation had no effect on cardiovascular disease. *Id.* at 000001.

951. The Supplementation with FOLate, vitamin B6 and B12 and/or OMega-3 fatty acids (SU.FOL.OM3) trial was a double blind randomized, placebo-controlled, secondary prevention trial designed to test the efficacy of folates supplementation (560 μg of 5-methyltetrahydrofolate) in combination with vitamin B-6 (3 mg) and B-12 (20 μg) and/or n-3 PUFA (600 mg of EPA and DHA at a ratio of 2:1) on fatal and non-fatal ischemic cardiovascular disease in a 2×2 factorial design. *See* PX 956 at 000002, Blacher et al., *Cardiovascular Effects of B-Vitamins and/or n-3 Fatty Acids: the Su.Fol.Om3 Trial*, 167 Int'l J. Cardiology 508 (2013) at AMRN03164798. A total of 2,501 patients with a past history of cardio- or cerebrovascular diseases were recruited between 2003 and 2007. *Id.* The subjects' median baseline TG levels were 114 mg/dL (1.29 mmol/L) in patients with a history of coronary revascularization, 126 mg/dL (1.42 mmol/L) in patients with a history of hard coronary event, and 108 mg/dL (1.22 mmol/L) in patients with no history of coronary event. *Id.* at 000003. There was a low use of conventional medical therapy such as statins or beta blockers in the subjects. The primary endpoint was a composite of non-fatal myocardial infarction, non-fatal ischemic stroke, or death from cardiovascular disease. After a mean follow-up period of 4.2 years, the trial did not demonstrate any effects of dietary supplementation with omega-3 fatty acids. *Id.* at 000001–02.

952. The Risk and Prevention (R&P) study was a double-blind, placebo-controlled clinical trial designed to evaluate the effects of omega-3 fatty acids in patients with a previous myocardial infarction or heart failure. *See* PX 949, Roncaglioni et al., *n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors*, 368 N. Eng. J. Med. 1800 (2013). 12,513 patients were randomly assigned to omega-3 fatty acids or placebo. 41% of the patients were on

statin therapy. *Id.* at 000001, 000005. At the beginning of the trial, the primary endpoint was the cumulative rate of death, nonfatal myocardial infarction, and non-fatal stroke. After 1 year, the primary endpoint was revised as the composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes. After a median of 5 years of follow-up, daily treatment with omega-3 fatty acids did not reduce cardiovascular mortality and morbidity. *Id.* at 000001.

953. The Age-Related Eye Disease Study 2 (AREDS2) was designed to determine whether long chain omega-3 fatty acids reduce the rate of cardiovascular disease. *See* PX 930, Bonds et al., *Effect of Long-Chain ω-3 Fatty Acids and Lutein + Zeaxanthin Supplements on Cardiovascular Outcomes: Results of the Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial*, 174 JAMA Internal Med. 763 (2014). 4,203 subjects were randomized to receive 1 g/day of omega-3 fatty acids (350 mg DHA + 650 mg EPA); 10 mg/day of lutein and 2 mg/day of zeaxanthin; omega-3 fatty acids, lutein, and zeaxanthin; or placebo. *Id.* at 000001. 44% of the subjects reported taking a statin medication at the start of the study. *Id.* at 000003. The primary endpoint was a composite outcome of time to the first event in a category of cardiovascular disease mortality and cardiovascular disease morbidity. After a median follow-up period of 4.8 years, omega-3 fatty acids did not reduce the risk of cardiovascular disease with or without a combination of lutein and zeaxanthin. *Id.* at 000001, 000003. The results of this trial were published in 2014.

954. The recently completed ASCEND trial ("A Study of Cardiovascular Events in Diabetes") evaluated the effects of receiving 1 g/day of omega-3 fatty acid capsules on the risk of serious vascular events in diabetic patients aged ≥ 40 years who did not have evidence of cardiovascular disease. *See* PX 961, Bowman et al., *Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus*, 379 N. Eng. J. Med. 1540 (2018). From June 2005 through July 2011, a total of 15,480 patients were randomized to receive 1 g/day of omega-3 fatty acid capsules or placebo capsules. 75% of the subjects were on statin therapy. The primary endpoint was the first serious vascular event, which was defined as a composite of nonfatal myocardial infarction or stroke

(excluding confirmed intracranial hemorrhage), transient ischemic attack, or vascular death excluding intracranial hemorrhage. The authors specifically acknowledged the great need for an agent to further reduce cardiovascular risk: "Since patients with diabetes have two to three times the risk of cardiovascular disease as the general population, a safe dietary supplement with even a modest protective effect could have a major public health benefit." *Id.* at 000002. However, after a follow-up period of 7.4 years, 1 g/day capsules of omega-3 fatty acids did not have a significantly lower incidence of serious vascular events than those who received placebo. Notably, the results of the ASCEND trial were published just a few months before the results of REDUCE-IT were announced.

955. Another recently completed trial, The Vitamin D and Omega-3 Trial (VITAL), was a randomized, placebo-controlled trial with a two-by-two factorial design of Vitamin D_3 (2,000 IU /day) and omega-3 fatty acids (1 g/day) in the primary prevention of cardiovascular disease and cancer. PX 962, Manson et al., *Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer*, 380 N. Eng. J. Med. 23 (2019). Randomization to receive omega-3 fatty acids, vitamin D, both active agent, or both placebos took place from November 2011 through March 2014. *Id.* at 3. 35% of the subjects were on statin therapy at the start of the study. The primary end points were major cardiovascular events (composite of myocardial infarction, stoke, and death from cardiovascular causes) and invasive cancer of any type. *Id.* at 000002. After a median follow-up period of 5.3 years, omega-3 fatty acid supplementation did not result in a lower incidence of major cardiovascular events than placebo. *Id.* at 000001.

956. In light of this long string of failed trials, the medical community expressed extreme skepticism about whether omega-3 fatty acid treatments would provide a cardiovascular benefit. For example, an article published in the *Journal of the American Medical Association* concluded in January 2018, based on the results of a meta-analysis of clinical trial results of omega-3 fatty acid preparations, that "omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events" and that there was "no support for current recommendations for the use of such supplements in people with a history of

coronary heart disease." PX 954 at 000001, Aung et al., *Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks: Meta-Analysis of 10 Trials Involving 77,917 Individuals*, 3 JAMA Cardiology 225 (2018) ("Aung") at AMRN03164724. And the Cochrane Collaboration concluded in July 2018 that, on the basis of its own meta-analysis, "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little." PX 953 at 000066, Abdelhamid et al., *Omega□3 Fatty Acids for the Primary and Secondary Prevention of Cardiovascular Disease*, 7 Cochrane Database Systematic Reviews 2018 1 (2018) ("Abdelhamid") at AMRN03164036.[27]

c) REDUCE-IT Trial

957. In contrast to the above clinical trials, the findings of REDUCE-IT are truly remarkable: REDUCE-IT reported that VASCEPA® significantly reduced major adverse events by 25% over and above statin therapy. *See supra* ¶ 178. No other clinical trial has shown such a large size effect for therapy on top of a statin. And the clinical benefits observed in REDUCE-IT far exceeded what would have been viewed as a success. For example, commentators had signaled that a 10 to 15 percent relative risk reduction would be clinically meaningful. PX 858, Hamilton et al., *Amarin surges as trial results exceed expectations*, Irish Times (Sept. 24, 2018). The 25 percent relative risk reduction seen with VASCEPA® in REDUCE-IT dwarfs that benchmark. Commentators have accordingly heralded the REDUCE-IT results as showing "a very impactful huge benefit." PX 714 at 000004, JEFFRIES LLC Key Opinion Leaders Conference Call, December 20, 2018, at AMRN-PEXP-0007341 (statement of Dr. Michael Shapiro) ("And here we have [a] very specific population and very specific formulation and very specific dose and really what appears to be a very impactful huge benefit on reducing cardiovascular events. . .").

[27] These publications notably failed to distinguish purified EPA from mixtures of DHA and EPA, and instead treated omega-3 fatty acids as a class, reflecting a longstanding view of omega-3 fatty acid treatments that did not differentiate EPA and DHA.

958. Moreover, REDUCE-IT showed that VASCEPA® is beneficial in reducing cardiovascular events in diabetics. *See supra* ¶ 179. Indeed, the ADA Guidelines were recently updated to acknowledge the results from the REDUCE-IT Clinical Study, and recommend that icosapent ethyl (VASCEPA®) be administered to patients with TGs in the range of 135–499 mg/dl. PX 162 at 000011–12, 2019 ADA Guidelines Supplement, at S112, comments 1 and 4 (AMRN-PEXP-0008666-67). Prior to the update, the 2019 ADA Guidelines did not recommend any TG-lowering medication for patients with triglycerides below 500 mg/dl. Late in March 2019, after convening an urgent meeting of a team of 14 leading experts in the field of diabetes and two representatives from the American College of Cardiology (ACC), the ADA standards of care were updated and published in a supplement. *See id.* at 000011 For the first time the ADA recommended consideration of the addition of icosapent ethyl to reduce cardiovascular risk in diabetic patients who have triglycerides below 500 mg/dl (135–499 mg/dl), are statin treated, and have ASCVD or other cardiac risk factors. This recommendation is based on the results of the REDUCE-IT trial**.** The ADA designated this update in March 2019 standards of care, a level "A" grade of scientific evidence, which is the highest level of scientific evidence that is granted by the ADA in its standard of care document, based on the caliber of the scientific data. *See id.* The ADA Guidelines stipulate further: "It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products." *Id.*

959. The results from REDUCE-IT are a stark departure from the clinical trial results of the other triglyceride-lowering products that, as discussed above, have failed to show clinically meaningful reductions in cardiovascular risk over and above the reduction already provided by statin therapy (and, in some cases, failed to show any benefit at all). *See supra* ¶¶ 907–25, 944–56. Accordingly, these findings have been met with great enthusiasm and surprise. *See infra* ¶ 1013.

960. Even prior to REDUCE-IT, there were numerous reasons to prescribe VASCEPA® as a treatment for severe hypertriglyceridemia. These reasons include that

VASCEPA® effectively lowers TG levels in persons with severe hypertriglyceridemia and therefore is presumed to reduce pancreatitis risk; that it does so without substantially increasing LDL-C; that it is extremely safe and well-tolerated with no known toxicity or serious side effects; that it is all-natural; that it causes minimal eructation, *i.e.*, fishy burps; that it requires no metabolic activation/conversion; that it has no known drug interactions (and can therefore be safely administered with other drugs, including statins); and that it can be eliminated by oxidative metabolism in the mitochondria of cells (*i.e.*, is consumed as fuel). In light of these benefits, doctors have for several years prescribed VASCEPA® as a first-line treatment for severe hypertriglyceridemia.

961. The REDUCE-IT results provide even further reason for doctors to make VASCEPA® the TG-lowering agent of choice for individuals with very high TG levels. Individuals with very high TG levels are at heightened risk of cardiovascular disease. *See, e.g.*, PX 834 at 000001, Christian, *Determining Triglyceride Reductions Needed for Clinical Impact in Severe Hypertriglyceridemia*, 127 The American Journal of Medicine 36 (2014) at AMRN00872270. Many individuals with very high TGs, for example, are diabetics—a group well-known to be at increased risk of cardiovascular disease. *See* PX 963 at 000001, Haffner et al., *Mortality From Coronary Heart Disease in Subjects With Type 2 Diabetes and in Nondiabetic Subjects With and Without Prior Myocardial Infarction*, 339 N. Eng. J. Med. 229 (1998) at AMRN-PEXP-0001467. Thus, while the most immediate concern for persons with severe hypertriglyceridemia is pancreatitis, addressing cardiovascular risk remains an important concern.

962. In multiple ways, VASCEPA® allows individuals with severe hypertriglyceridemia to make progress in reducing cardiovascular risk at the same time that they are addressing pancreatitis risk.

963. First, there is a strong basis to conclude that such individuals will experience the cardiovascular benefit observed in REDUCE-IT when their TG levels are 500 mg/dl or greater, even though subjects in the REDUCE-IT trial had TG levels ranging from 135 mg/dl to 499

mg/dl at enrollment. This is in part because the cardiovascular benefits of VASCEPA® in REDUCE-IT were consistent across different baseline triglyceride levels: persons with baseline TG levels below 200 mg/dl showed a similar reduction in cardiovascular risk as persons with TG levels above 200 mg/dl; persons with baseline TGs below 150 mg/dl showed a similar benefit as those with baseline TGs above 150 mg/dl; and patients in the highest tertile of baseline TGs derived at least as great a cardiovascular benefit from VASCEPA® as individuals in the middle and lower TG tertiles. PX 272 at 000010, Bhatt NEJM 2019 at AMRN-PEXP-0000698; PX 1189 at 000019, 000177–78, 000181, 000186, 000195–96, 000204–05, 000212, REDUCE-IT Clinical Study Report at AMRN03172272, AMRN03172430–31, AMRN03172434, AMRN03172439, AMRN03172448–49, AMRN03172457–58, AMRN03172465. Patients in the highest tertile of baseline TG levels had baseline TG levels that ranged from 250 mg/dl to 1,401 mg/dl.[28] *Id.* at 000195–96. The relative risk of experiencing a primary endpoint event in this group was reduced by 32% compared to placebo, which was a nominally greater risk reduction, and not statistically different from, the relative risk reduction experienced by subjects in the tertiles with lower baseline TG levels. *Id.* at 000188.

964. Additionally, the significantly lower risk of major cardiovascular events with VASCEPA® appeared to occur irrespective of the attained TG level at 1 year (whether above or below 150 mg/dl). PX 1189 at 000007, 000010, REDUCE-IT Clinical Study Report at AMRN03172260, AMRN03172263; PX 272 at 000007, 000010, Bhatt NEJM 2019 at AMRN-PEXP-0000695, AMRN-PEXP-0000698. This means that there are mechanisms other than, and in addition to, TG-lowering that may be responsible for a remarkable 25% RRR in cardiovascular events observed in REDUCE-IT among statin-treated patients with controlled

[28] Some subjects in the REDUCE-IT trial had TG levels of 500 mg/dl or greater at randomization—when study medication was first administered—because their TG levels increased between the time they qualified for inclusion (when TG levels could not exceed 499 mg/dl), and randomization, when they began to take the study medication. *See* PX 1189 at 000055–57, 000196, REDUCE-IT Clinical Study Report at AMRN03172308–10, AMRN03172449.

LDL (though further analysis may show that TG-lowering plays some role in cardiovascular risk reduction). PX 272 at 000010–11, Bhatt NEJM 2019 at AMRN-PEXP-0000698–99. Currently, mechanisms responsible for the clinical benefits of EPA are not fully known—and certainly were not known in 2008—but several lines of emerging scientific evidence suggest that EPA achieves its dramatic and unexpected reduction in cardiovascular risk through mechanisms including membrane stabilization,[29] endothelial function improvement,[30] plaque stabilization and regression,[31] and anti-inflammatory effect.[32] These mechanisms are unrelated to the known TG-lowering effects of EPA, and provide further reason to conclude that patients with TGs levels of

[29] Destabilization of cell membranes can contribute to atherogenesis, and recent studies have shown that EPA has the effect of stabilizing the cell membrane. *See* PX 500, Mason & Jacob, *Eicosapentaenoic Acid Inhibits Glucose-Induced Membrane Cholesterol Crystalline Domain Formation Through a Potent Antioxidant Mechanism*, Biochimica et Biophysica Acta 1848:502–509 (2015); PX 507, Mason et al., *Eicosapentaenoic Acid Reduces Membrane Fluidity, Inhibits Cholesterol Domain Formation, and Normalizes Bilayer Width in Atherosclerotic-Like Model Membranes*, Biochimica et Biophysica Acta 1858:3131–3140 (2016); PX 529, Sherratt & Mason, *Eicosapentaenoic Acid and Docosahexaenoic Acid Have Distinct Membrane Locations and Lipid Interactions as Determined by X-ray Diffraction*, Chemistry and Physics of Lipids 212:73–79 (2018).

[30] Endothelial dysfunction is causally related to atherosclerosis and is associated with increased cardiovascular risk. It has been shown recently that EPA can reverse parameters of endothelial dysfunction. *See* PX 522, Mason et al., *Eicosapentaenoic Acid Improves Endothelial Function and Nitric Oxide Bioavailability in a Manner that is Enhanced in Combination with a Statin*, Biomedicine & Pharmacotherapy 103:1231–1237 (2018).

[31] Plaque stabilization and regression reduce cardiovascular risk by preventing the plaque from rupturing, and by reducing the volume of thrombogenic material in the plaque. Recent studies have shown that EPA promotes stabilization and regression of plaque. *See* PX 501, J.R. Nelson et al., *Potential Benefits of Eicosapentaenoic Acid on Atherosclerotic Plaques*, Vascular Pharmacology 91:1–9 (2017); PX 534, Watanabe et al., *A Randomized Controlled Trial of Eicosapentaenoic Acid in Patients with Coronary Heart Disease on Statins*, J. of Cardiology 70:537–544 (2017).

[32] Inflmmation promotes atherogenesis and atherothrombotic events. Studies have shown that EPA reduces hs-CRP, which is a biomarker of inflammation. *See* PX 505, Bays et al., *Icosapent Ethyl, a Pure Ethyl Ester of Eicosapentaenoic Acid: Effects on Circulating Markers of Inflammation from the MARINE and ANCHOR Studies*, Am. J. Cardiovasc. Drugs 13:37–46 (2013); PX 955 at 000038, Bhatt et al., *Supplement to: Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia*, N. Eng. J. Med. at AMRN03164772.

at least 500 mg/dl experience the dramatic cardiovascular risk reduction observed in REDUCE-IT.

965. The conclusion that the cardiovascular benefits observed in REDUCE-IT apply in individuals with TGs of at least 500 mg/dl is also informed by the results of the MARINE trial. Given the results of the MARINE trial, it is now known that VASCEPA® will not substantially raise LDL-C levels in the very high TG population, and thus there is no concern that increases in LDL-C could confound or nullify the cardiovascular benefits seen in the REDUCE-IT population. Prior to VASCEPA® and the MARINE trial, a person of ordinary skill in the art would have expected that there would be a large increase in LDL-C when purified EPA was used in the very high TG population (along the lines of what was observed in the prior art with LOVAZA®), and therefore not have expected that the very high TG group would experience cardiovascular benefits even if individuals with lower TGs were understood to enjoy such benefits. Now, however, with the benefit of the findings of MARINE and REDUCE-IT, there is a sound basis to so conclude.

966. Indeed, FDA itself has recognized that the REDUCE-IT results apply to patients with TGs of at least 500 mg/dl. After reviewing the REDUCE-IT results, FDA very recently expanded the approved use of VASCEPA® to include reduction in cardiovascular risk in persons with TG levels over 150 mg/dl, including persons with very high TGs. The inclusion of patients with very high TGs in VASCEPA®'s cardiovascular risk reduction indication demonstrates FDA's view that the REDUCE-IT results apply to individuals with TGs of at least 500 mg/dl. Moreover, in approving the expanded indication, FDA removed the Limitaton of Use that stated, "The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined," thus recognizing VASCEPA®'s cardiovascular benefit in patients with very high TGs. *Compare* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169, *with* PX 1186 at 000002, VASCEPA® Prescribing Information (2019) at AMRN03174954. VASCEPA® is now the first FDA approved drug to reduce cardiovascular risk among patients with elevated TG levels as an add-on to maximally

tolerated statin therapy, and the only drug approved for treatment of severe hypertriglyceridemia that has also been shown to provide cardiovascular benefit to patients on top of a statin.

967. Additionally, regardless of whether VASCEPA® lowers cardiovascular risk in individuals while their TG levels are 500 mg/dl or greater, REDUCE-IT still provides a powerful reason for doctors to prescribe VASCEPA® to individuals with severe hypertriglyceridemia. Because VASCEPA® is effective in lowering triglycerides, it will bring the TG levels of many individuals who originally start with TG levels above 500 mg/dl to TG levels below 500 mg/dl, such as an individual who starts with 650 mg/dl, takes VASCEPA®, and then has her TG levels brought down to 450 mg/dl. At that point, such individuals will effectively have the TG levels required for inclusion in REDUCE-IT. And at that point, at the very least, they will benefit from cardiovascular risk reduction to the same degree as the REDUCE-IT population.

968. Furthermore, prescribing VASCEPA® to individuals with very high TGs from the outset avoids the need to switch medication later, once TG levels drop below 500 mg/dl, and it will allow such individuals to bank time taking VASCEPA®, which will help to bring about cardiovascular benefits sooner. As both the MARINE and ANCHOR Clinical trials showed, individuals taking a daily dose of 4g of VASCEPA® over twelve weeks experience changes in their biochemistry beyond reductions of triglycerides, including changes in VLDL-C, Lp-PLA2, ApoB, non-HDL as compared to placebo. *See* PX 807 at 000105, MARINE Clinical Study Report at AMRN00053561; PX 942 at 000005, Ballantyne at AMRN03144842. The buildup of EPA during this 12-week period provides beneficial physiologic changes to the cardiovascular environment, bringing people closer to the point at which people will begin to see reduced risk of cardiovascular events.

969. For those patients with very high TGs not taking a statin, moreover, it is reasonable to conclude that VASCEPA® will provide cardiovascular benefits. Although the mechanism by which VASCEPA® reduces cardiovascular risk is not fully known, VASCEPA®'s

benefits do not depend upon statin use. Indeed, much of the surprise from REDUCE-IT is that VASCEPA® dramatically reduces cardiovascular risk *on top of* statin use.[33]

970. Prior to REDUCE-IT, numerous doctors prescribed VASCEPA® as a first-line treatment for severe hypertriglyceridemia. The REDUCE-IT results will lead doctors to prescribe VASCEPA® more frequently, and as a first-line treatment. VASCEPA® is now the only logical TG-lowering agent for individuals with severe hypertriglyceridemia. It is a cost-effective, well-tolerated medication that lowers TGs, avoids substantial LDL-C increases, and provides a substantial reduction in cardiovascular risk, over and above the risk reduction provided by statin therapy. By contrast, all other TG-lowering drugs have serious limitations in terms of safety, tolerability, or increases in LDL-C, and have not demonstrated a clinical cardiovascular benefit over and above appropriate statin therapy.

971. VASCEPA® is the first approved TG-lowering agent that significantly lowers risk of cardiovascular events over and above the reduction provided by appropriate statin therapy. As demonstrated in REDUCE-IT, VASCEPA® provides a dramatic reduction in cardiovascular risk (relative risk reduction of approximately 25%) over and above the risk reduction provided by statin therapy that brought LDL-C levels below 100 mg/dl.

972. Given the results from the MARINE study showing that VASCEPA® does not raise LDL-C in persons with severe hypertriglyceridemia, REDUCE-IT provides a sound basis to conclude that patients with triglyceride levels exceeding 500 mg/dl would benefit from the same risk reduction experienced by subjects in the REDUCE-IT trial. As noted above, REDUCE-IT suggests that cardiovascular risk reduction with purified EPA is consistent across different baseline triglyceride levels, including in the upper tertile of patients, which included some patients with baseline TGs of at least 500 mg/dl. *See supra* ¶ 963. And moreover, FDA's

[33] The cardiovascular risk reduction provided by statins is achieved largely by lowering LDL-C. But VASCEPA® is effectively LDL-C neutral, and therefore achieves its cardiovascular risk reduction through some other means. Even if VASCEPA® did reduce cardiovascular risk through the same mechanism as statins, moreover, it would provide cardiovascular benefit in the absence of a statin, because it would serve as a replacement for the statin in such instance.

approval of VASCEPA®'s expanded indication reflects FDA's view that the cardiovascular benefits observed in the REDUCE-IT trial will extend to the very-high TG population. *See supra* ¶ 187, 966.

973. Additionally, as noted above, because VASCEPA® lowers below 500 mg/dl the TG levels of many people who initially have very high triglycerides, it at a minimum allows these individuals to benefit from cardiovascular risk reduction to the same extent as the population studied in REDUCE-IT once their TG levels fall below 500 mg/dl. VASCEPA® therefore has met a long-felt need in multiple respects.

974. VASCEPA®'s meeting of long-felt needs is linked to the features of the Asserted Claims, as VASCEPA®'s ability to meet these needs for the very high TG population are linked to, for example, its composition (at least 96% EPA and substantially no DHA), its daily dose of 4g/day over a period of 12 weeks or more, its avoidance of substantial increase in LDL-C in patients with TG levels of at least 500 mg/dl, its lowering of TGs, and its avoidance of an increase, or reduction in, apoB. These needs were not met by other medications, including niacin, fibrates, and other omega-3 fatty acid formulations such as DHA/EPA mixtures.

B. Failure of Others

975. Failure of others to solve a problem addressed by an invention suggests that the invention was not obvious, as others would have solved the problem sooner if the solution had been obvious. Here, failure of others supports the non-obviousness of VASCEPA® and the Asserted Claims.

976. As discussed above, prior TG-lowering agents all had significant limitations in the very high TG group, and other efforts to address those concerns in a single product failed. *See supra* ¶¶ 126–50.

977. For example, AstraZeneca pursued the omega 3-fatty acid treatment EPANOVA®, which contained approximately 550 mg EPA and 200 mg DHA in each 1 gram capsule, but EPANOVA® 4g increased LDL-C by 15% in patients with severe hypertriglyceridemia, and the proposed product label therefore warned that "LDL-C levels

should be monitored periodically during therapy with EPANOVA." PX 849 at 000003, EPANOVA® Label (2014) ("EPANOVA® Label 2014") at AMRN03129986, Table 1.

978. Contrary to what Defendants will argue, other products had not met the need for a well-tolerated TG-lowering agent that lowered TGs without substantially increasing LDL-C in patients with severe hypertriglyceridemia. For example, Defendants may argue that the EPA product Epadel met the long-felt need. As discussed above, references such as Mori 2000, Kurabayashi, and Hayashi did not disclose that high purity EPA lowers triglycerides in persons with very high triglycerides without substantially increasing LDL-C in persons with very high triglycerides. Those publications dealt with populations with triglyceride levels of less than 500 mg/dl. *See supra* ¶¶ 770–83. Those references—or any other reference cited by Defendants—did not establish that Epadel avoids substantial LDL-C increases in persons with severe hypertriglyceridemia, nor would they have created such an expectation. *See id.* Likewise, Defendants will argue that the combination of LOVAZA® plus a statin met the long-felt need. However, the combination of LOVAZA® and statins was undesirable. *See supra* ¶¶ 899–901. Having to combine LOVAZA® with a statin added a pill burden—increasing expense and demands for patient compliance. Moreover, the increases associated with LOVAZA® blunted the beneficial LDL-C lowering effects of the statin, running counter to the important secondary treatment goal of minimizing risk of cardiovascular disease in persons with very high triglycerides. *See id.* Furthermore, contrary to what Defendants will contend, statins often could not offset the LDL-C increases caused by LOVAZA® in persons with very high triglycerides, such as instances in which a patient was statin intolerant, or where the LDL-C increase was too large (median 49.3% compared to placebo) for the statin to offset the increase. *See supra* ¶¶ 901.

979. Furthermore, in stark contrast to VASCEPA®, all other triglyceride-lowering products—fibrates, niacin, and other omega-3 fatty acid preparations—have failed to demonstrate clinically meaningful reductions in cardiovascular risk over and above the reduction already provided by appropriate statin therapy (and some cases, failed to show any cardiovascular risk reduction). The trials are discussed above and include FIELD, ACCORD,

AIM-HIGH, HPS2-THRIVE, OMEGA, Alpha Omega, SU.FOL.OM3, DOIT, ORIGIN, Risk and Prevention, AREDS2 ASCEND, and VITAL. *See supra* ¶¶ 907–925, 944–56.

980. Numerous commentators have recognized that others failed where VASCEPA® succeeded. *See, e.g.*, PX 959 at 000002, Kastelein et al., *FISHing for the Miracle of Eicosapentaenoic Acid*, N. Eng. J. Med. (2018) ("Kastelein") at AMRN03168529 ("[A]fter a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events."); PX 857 at 000002, Nisen, *Fish-Oil Heart Medicine Is Rarest of Drug Breakthroughs*, Bloomberg Opinion (Sep. 24, 2018) at AMRN03163945 ("But many previous fish-oil trials have failed. VASCEPA®'s purity enables a higher dose without raising cholesterol, as other fish oils can."); PX 858 at 000001, Hamilton at AMRN03163951 ("[W]ary after the failure of several fish oil trials for rival products, the FDA has been minded until now to grant VASCEPA® only niche status."); PX 875 at 000002, Fidler, *Amarin Soars as Fish Oil Pill Cuts Risk of Strokes in Long-Awaited Study*, Xconomy (Sept. 24, 2018) at AMRN-PEXP-0001386 ("For years, drugmakers have tried to show that adding fish oil to the mix can help because it can lower triglycerides, a risk factor for heart disease. But several clinical studies have failed to prove the worth of fish oil."); PX 859 at 000003, Neale, *REDUCE-IT: Prescription Fish Oil Prevents CV Events in Patients With High Triglycerides*, tctMD (Nov. 10, 2018) at AMRN0163965 ("Even so, nearly all prior trials evaluating a variety of triglyceride-lowering therapies—including extended-release niacin, fibrates, cholesteryl ester transfer protein inhibitors, and omega-3 fatty acids—have failed show reductions in cardiovascular events.").

981. Contrary to what Defendants will argue, the JELIS trial did not demonstrate that Epadal previously met the long-felt need for a triglyceride-lowering agent that significantly lowered cardiovascular risk over and above appropriate statin therapy in persons with severe hypertriglyceridemia. *See supra* ¶¶ 930–43. JELIS was an open-label, non-placebo controlled trial, whose positive outcome was driven largely, if not entirely, by a single parameter—unstable angina—that was subjective and susceptible to bias. *See id.* Indeed, FDA was troubled by the design flaws of JELIS, and did not believe that JELIS was sufficient to establish that high purity

EPA significantly reduced residual cardiovascular risk. *See supra* ¶¶ 941–42. Moreover, as noted above, the prior art taught both the problems with unblinded studies generally and the specific concern with use of subjective endpoints in such studies. *See supra* ¶ 934. A person of skill in the art would have been highly skeptical of the JELIS results.

982. By its very design, the JELIS trial could not have answered the question of whether Epadel met the need for a triglyceride-lowering agent that reduced residual cardiovascular risk over and above appropriate statin therapy. Appropriate statin therapy requires dosing of the statin to the point at which LDL-C levels are well-controlled—a level that has been generally been understood to be less than 100 mg/dl. *See supra* ¶ 178. But the LDL-C levels in JELIS were not well-controlled, and the statin doses administered were quite low. *See supra* ¶¶ 931, 942.

983. The notion that JELIS demonstrated that Epadel had already met the long-felt need for a triglyceride-lowering agent that significantly reduced residual cardiovascular risk is belied by the widespread surprise and enthusiasm in late 2018, after publication of the REDUCE-IT results. *See infra* ¶¶ 1013. For instance, in an editorial in the *New England Journal of Medicine*, the authors welcomed the REDUCE-IT results showing a substantial cardiovascular benefit with VASCEPA® with "surprise, speculation, and hope . . . . After a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events." PX 959 at 000001, Kastelein at AMRN03168528. And leading doctors observed that REDUCE-IT was a "game changer," giving rise to "a new option that impacts cardiovascular outcomes to a greater extent than just throwing on more LDL cholesterol lowering drugs." *See infra* ¶ 1013. The results of REDUCE-IT would not have been welcomed with such enthusiasm and surprise if the need for a triglyceride-lowering agent that significantly reduced cardiovascular risk had already been solved years earlier by Epadel in JELIS.

984. Nor, if Epadel had satisfied this need, would omega-3 fatty acids, including high purity EPA, have been viewed with major skepticism in early 2018, prior to the publication of

the REDUCE-IT results. *See infra* ¶¶ 990–91. For example, that an article in *JAMA Cardiology* published just months before REDUCE-IT concluded that there was "no support for current recommendations for the use of [omega-3 fatty acid] supplements in people with a history of coronary heart disease," including purified EPA, even though the authors were aware of the JELIS result. PX 954 at 000001, Aung at AMRN03164724. If the medical field believed from JELIS that Epadel significantly lowered residual cardiovascular risk, as Defendants will contend, there would have been no such blanket rejection of omega-3 fatty acids.

985. FDA's 2013 rejection of Amarin's proposed additional indication for VASCEPA® further undercuts Defendants' contention that Epadel met the long-felt need for a triglyceride-lowering agent that significantly reduced residual cardiovascular risk. As noted above, Amarin had shown in the ANCHOR trial that VASCEPA® lowered triglycerides in persons with baseline TGs of 200–499 mg/dl, and on that basis sought an indication to administer VASCEPA® to statin-treated patients in this TG range, on the theory that VASCEPA® may provide a cardiovascular benefit to such patients. *See supra* ¶ 172 . But FDA declined to grant the indication without completion of the REDUCE-IT trial, concluding that the available evidence at the time—which included the results from the JELIS trial—was insufficient to conclude that high purity EPA would provide a significant incremental cardiovascular benefit over and above appropriate statin therapy. *See supra* ¶ 173.

C. Skepticism

986. Skepticism about an invention, both before and after the invention is made, is evidence that an invention was not obvious. Skepticism is further evidence that VASCEPA® and the Asserted Claims were not obvious, as there was significant initial skepticism about VASCEPA®.

987. To begin with, there was skepticism about whether VASCEPA® could avoid a substantial increase in LDL-C in patients with very high TG levels. For example, Amarin hosted a panel of experts in December 2008 to elicit their views regarding AMR101, which was the development project that led to VASCEPA®. One panelist told Amarin that "LDL-C is likely to

go up as it does with virtually all [TG] lowering therapies in this group of patients [having very high triglycerides]" and another told Amarin that it should be "very careful" about working with patients whose baseline TGs were between 500 and 650 mg/dl because they would have "relatively high IDL and therefore treatment is likely to increase the conversion of IDL to LDL in these patients—thus pushing up LDL-C." PX 754 at 000002, *Ian Osterloh's Notes from Amarin's Expert Panel Meeting 12th December 2008, Boston* at AMRN01531056; *see also* Osterloh Dep. 183:15–187:4, Nov. 5, 2018 (discussing skepticism of experts at Amarin's 2008 Expert Panel Meeting). As these comments reflect, there was initial skepticism that VASCEPA® would be able to lower TGs in the very high TG population without a substantial increase in LDL-C.

988. And even after initial results of VASCEPA®'s MARINE trial were announced, the results were met by some with caution. For example, expert Dr. Darren McGuire observed that the "early results [we]re intriguing" because "[a]t the end of the day, if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage," but believed that it was necessary to "insert a dose of caution." PX 425 at 00001, O'Riordan at AMRN-PEXP-0009483.

989. There was also doubt about the apoB lowering effect of VASCEPA® after the MARINE trial results were published. For example, speaking about the MARINE Clinical Trial to *Heartwire*, a cardiology publication, Dr. Roger Blumenthal of Johns Hopkins University Medical Institute stated that fish oils "do not affect levels of [apo-B]," PX 425 at 000001, O'Riordan, AMRN-PEXP-0009483, thereby expressing skepticism that VASCEPA® could do what it has been proven to do: reduce apoB.

990. More generally, there was skepticism about whether VASCEPA®, along with other omega-3 fatty acid treatments, would be of any benefit in preventing coronary heart disease or otherwise reducing cardiovascular risk. Physicians and publications prior to REDUCE-IT expressed general doubt on the subject, going as far as stating in early 2018, for example, that there was no support for use of VASCEPA® or other omega-3 fatty acid preparations in people

with cardiovascular risk. *See, e.g.*, PX 954 at 000001, Aung at AMRN03164724 (concluding on the basis of a meta-analysis that "omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events" and that there was "no support for current recommendations for the use of such supplements in people with a history of coronary heart disease."); PX 953 at 000066, Abdelhamid at AMRN03164036 (concluding on the basis of a meta-analysis that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little."). And numerous practitioners and medical experts believed that REDUCE-IT would fail to demonstrate a clinical cardiovascular benefit. *See, e.g.*, PX 951 at 000002, Feuerstein, *Amarin Fish Oil Capsule Shows Dramatic Benefit for Cardiovascular Patients, Potentially Upending Market*, STAT News (Sept. 24, 2018) at AMRN03163954 ("All previous outcomes studies investigating different formulations of omega-3-containing products have been unsuccessful, leading to heavy skepticism in the cardiology community about the medicinal value of these supplements."); *id*. at 2 (statement of Dr. Norman Lepor) ("I went into this study not convinced that Vascepa would make a difference, but these results will definitely change my practice and the way I treat patients."); *id*. (statement of Dr. Ethan Weiss) ("I thought the Vascepa study would be negative, colored by all the prior failed studies so I'm surprised. I'm willing to eat my shoe on this one. This could be really beneficial to people.").

991. REDUCE-IT has put all of that skepticism to rest, showing that use of VASCEPA® substantially lowers cardiovascular risk over and above the risk reduction provided by statins alone.

D. Unexpected Results

992. Evidence that an invention has unexpected benefits is evidence of non-obviousness, because that which is surprising tends to not be obvious. VASCEPA®, and the Asserted Claims whose VASCEPA®'s use embodies, has a number of unexpected benefits.

993. *First*, at the time of the invention, a person of ordinary skill in the art would have expected that a drug containing at least 96% EPA, such as VASCEPA®, would substantially increase LDL-C in the very high TG population, on the order of the LDL-C increase seen with LOVAZA® in the same population. But surprisingly, VASCEPA® showed no such increase in LDL-C.

994. In patients with very high TGs, use of LOVAZA® resulted in an increase in LDL-C of over 40%. *See, e.g.*, DX 1578 at AMRN01187779, LOVAZA® Label 2007 at Table 2 (showing placebo-adjusted LDL-C increase of 49.3% and increase in LDL-C from baseline of 44.5%). A person of ordinary skill in the art in March 2008 would have expected a similar increase in LDL-C with an omega-3 fatty acid therapy containing at least 96% EPA, and would have based his or her expectation of such increase on the experience with LOVAZA®.

995. At the time of the invention, LOVAZA® was the closest prior art to the Asserted Claims, as it was the only omega-3 fatty acid product approved for use in the very high TG population. Moreover, there was no other prior art that reported the effect on LDL-C of any omega-3 fatty acid preparation in the very high TG population, other than LOVAZA®.

996. Additionally, while the mechanism for lowering TGs was not completely understood, a person of ordinary skill in the art would have believed that an omega-3 fatty acid preparation containing at least 96% EPA would increase LDL-C in the very high TG population for the same reason that person would have understood that LOVAZA® increased LDL-C in that population. As of March 2008, skilled artisans believed that omega-3 fatty acid preparations lowered TGs at least in part by converting VLDL to LDL. *See supra* ¶¶ 114–16. Because individuals with severely elevated TGs levels typically have high levels of VLDL, a person of ordinary skill would have expected that decreasing TG levels would necessarily involve converting large numbers of VLDL particles to LDL particles, thus invariably increasing LDL and LDL-C.

997. Unexpectedly, however, VASCEPA® produced no such increase. In the MARINE trial, VASCEPA® had a non-significant placebo-adjusted decrease in LDL-C of 2.3%.

See PX 807 at 000081, MARINE Clinical Study Report at AMRN00053537, Table 15; PX 504 at 000005, Bays 2011 at AMRN03144931, Table 3 Continued; *see also* PX 833 at 000006, Friedewald et al., *The Editor's Roundtable: Hypertriglyceridemia*, 112 Am. J. Cardiol. 1133 ("Friedewald") at AMRN00870637 ("**Dr. Friedewald:** Why were the . . . LDL-C results a surprise? **Dr. Bays:** They were a surprise because prior studies . . . in patients with very high TGs at baseline, EPA and DHA increase LDL-C by as much as 45%"); Bays Dep. 155:23-56:2, Nov. 5, 2018 ("[M]y expectation was, prior to getting the results of the MARINE trial, is that the LDL cholesterol levels would rise after administration of AMR101 in patients with very high triglyceride levels.").

998. Contemporaneous evidence around the time of the invention confirms that VASCEPA®'s avoidance of an LDL-C increase was unexpected. For example, in December 2008, Amarin hosted a panel of experts to share their views regarding AMR101, which was the development project that led to VASCEPA®. One panelist told Amarin that "LDL-C is likely to go up as it does with virtually all [TG] lowering therapies in this group of patients [having very high triglycerides]." PX 754 at 000002, *Ian Osterloh's Notes from Amarin's Expert Panel Meeting 12th December 2008, Boston*, at AMRN01531056; *see also* Osterloh Dep. 183:15–187:4, Nov. 5, 2018. Another panelist also told Amarin that it should be "very careful" about working with patients whose baseline TGs were between 500 and 650 mg/dl because they would have "relatively high IDL and therefore treatment is likely to increase the conversion of IDL to LDL in these patients—thus pushing up LDL-C." PX 754 at 000002, *Ian Osterloh's Notes from Amarin's Expert Panel Meeting 12th December 2008, Boston* at AMRN01531056. As these comments reflect, there was no expectation that VASCEPA® would be able to lower TGs in the very high TG population without a substantial increase in LDL-C.

999. VASCEPA®'s unexpected avoidance of a substantial increase in LDL-C is beneficial because, as explained above, LDL-C is associated with cardiovascular risk. Therefore, increases in LDL-C increase cardiovascular risk, interfere with use of statins, and undermine the secondary treatment goal of lowering LDL-C in people with very high TGs.

1000. *Second*, VASCEPA® significantly and unexpectedly lowered apoB levels by 8.5% compared to the placebo group in very high TG patients. *See* PX 504 at 000003–05, Bays 2011 at AMRN03144929–31; PX 807 at 000079, MARINE Clinical Study Report at AMRN00053535; *see also* PX 940 at 000007, VASCEPA® Prescribing Information (2017) at AMRN03132174. The atherogenic lipoproteins (VLDL, IDL, and LDL) contain a single apoB molecule. Consequently, measurements of apoB represent a surrogate for the total number of circulating atherogenic lipoproteins. ApoB levels are therefore important because they are thought to be a sensitive predictor of coronary heart disease risk. In addition, apoB had been identified as of 2008 in the field of diabetes as a lipid parameter to focus on to reduce the risk of cardiovascular disease. *See* PX 398 at 000019, 2009 ADA Guidelines at S31 (AMRN-PEXP-0000740) ("In 2008, a consensus panel convened by ADA and the American College of Cardiology recommended a greater focus on non-HDL cholesterol and apoB in patients who are likely to have small LDL particles, such as people with diabetes."). Given the importance of this lipid parameter in diabetic patients, this result was a significant and unique advance for treatment of diabetic patients with severe hypertriglyceridemia.

1001. In contrast to VASCEPA®, LOVAZA®/OMACOR®, the closest prior art, showed no difference between a placebo-control group and the treatment group with respect to apoB levels. This was revealed in two U.S. studies that examined the effect of LOVAZA® on apoB levels in patients with TG $\geq$ 500 mg/dl, whose results were reported in the LOVAZA® Approval Package showed that apoB did not change compared to control in patients with TG $\geq$ 500 mg/dl. *See* PX 38 at 001064, File History of U.S. Patent No. 8,293,727 at AMRN03059169; *see also* PX 939 at 000025, LOVAZA® Statistical Review at AMRN03059189, Figure 7; *id*. at 000033, Figure 14; PX 57 at 000004–05, Bays Decl. III, ¶¶ 16–17, AMRN03059818–19 ("As can be seen in the figure below . . . when Lovaza . . . was given to subjects with very high triglycerides . . . apoB did not change compared to control. . . . .Similarly with regard to the other studies reported in Table 14 . . . , none demonstrated that Lovaza significantly reduced apoB compared to control.")

1002. A person of ordinary skill in the art would have found VASCEPA®'s reduction in apoB unexpected. *See* PX 833 at 000006, Friedewald at AMRN00870637 ("**Dr. Bays:** Two surprising results of MARINE were a reduction in serum apoB and failure of LDL-C to rise. **Dr. Friedewald:** Why were the apoB and LDL-C results a surprise? **Dr. Bays:** They were a surprise because prior studies of EPA plus DHA showed little change in apoB, and in patients with very high TGs at baseline, EPA and DHA increased LDL-C by as much as 45%.").

1003. *Third*, VASCEPA® unexpectedly dramatically reduced cardiovascular risk over and above the risk reduction provided by appropriate statin therapy—a reduction that only became clear after publication of results from the REDUCE-IT trial. Numerous physicians and other commentators have expressed surprise at the results from REDUCE-IT. *See, e.g.*, PX 959 at 000001, Kastelein at AMRN03168528 ("We welcome these results with surprise, speculation, and hope. Most surprising was the difference between the results of REDUCE-IT and those of many previous trials of n–3 fatty acids."); PX 952 at 000001, O'Connor, *Fish Oil Drug May Prevent Heart Attack and Strokes in High-Risk Patients*, The New York Times (Sept. 25, 2018) at AMRN03163960 ("'I'm very surprised by the magnitude of the results, which quite frankly are large,' said Dr. Michael J. Blaha, the director of clinical research at the Ciccarone Center for the Prevention of Heart Disease at Johns Hopkins Medical School, who was not involved in the study. 'My expectations were very low. A lot of people are legitimately surprised by this.'"); PX 951 at 000003, Feuerstein, *Amarin's stock soars after its fish oil capsule was found to dramatically reduce cardiovascular risks*, STAT News (Sept. 24, 2018) at AMRN03163955 ("'I went into this study not convinced that Vascepa would make a difference, but these results will definitely change my practice and the way I treat patients,' said Dr. Norman Lepor, a cardiologist at Cedars-Sinai Medical Center in Los Angeles. Lepor enrolled patients in the Vascepa study."); PX 858 at 000001, Hamilton et al., *Amarin surges as trial results exceed expectations*, Irish Times (Sept. 24, 2018) at AMRN03163951 ("Amarin has spent the best part of a decade trying to persuade regulators of the efficacy of its drug. However, wary after the failure of several fish oil trials for rival products, the FDA has been minded until now to grant Vascepa only niche

status."); PX 715 at 000003, Gingerich, *Icosapent Ethyl Reduces Cardiovascular Death Risk 20% in REDUCE-IT Trial*, MD Magazine (Nov. 11, 2018) at AMRN-PEXP-0007480 (quoting *Michael Miller, MD: REDUCE-IT Trial*, YouTube (Nov. 2018)) ("Well the results we think were quite surprising and prior studies in this space—the cholesterol-lowering space—have shown that it is very difficult to reduce risk of future events in people who already have established statin background. So, that's the first thing we've understood because there have been a number of trials that have had negative results.").

1004. As noted above, REDUCE-IT revealed that VASCEPA® provides a 25% relative residual risk reduction in the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, and a 26% relative risk reduction in the secondary composite end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke compared to those taking statin and placebo. PX 272 at 000009, Bhatt NEJM 2019 at AMRN-PEXP-0000697; PX 1189 at 000132, 000134, REDUCE-IT Clinical Study Report at AMRN03172385, AMRN03172387. This is a dramatic benefit, as no previous clinical trial has shown such an effect on top of a statin. These results are unexpected in view of the long line of prior trials had failed to show that TG-lowering products, including n-3 fatty acid preparations, would significantly reduce cardiovascular risk in high-risk patients over and above the risk reduction provided by appropriate statin therapy. *See supra* ¶¶ 907–25, 944–56.

1005. Defendants will argue that the JELIS trial established that Epadel significantly reduced residual cardiovascular risk, but as reflected by the surprise with which the REDUCE-IT results were met, that is not generally how the medical community saw it. FDA concluded that JELIS did *not* establish that EPA reduces residual cardiovascular risk over and above appropriate statin use, and the results of REDUCE-IT would not have been met with such surprise if JELIS had been understood to establish cardiovascular benefits with high purity EPA a decade earlier. *See supra* ¶¶ 941–42, 1013.

1006. FDA did not understand JELIS to establish a significant cardiovascular benefit at least in part because of its methodological flaws, and a person of ordinary skill in the art in March 2008 would have shared the same understanding, as JELIS was a non-placebo-controlled open-label trial whose overall positive outcome was driven primarily if not exclusively by a single subjective endpoint—unstable angina—that was susceptible to, and may well have been skewed by, bias. *See supra* ¶¶ 933–42. Nor, given the low statin doses and uncontrolled LDL-C levels of the subjects in JELIS, would JELIS have created any expectation that EPA would provide significant cardiovascular risk reduction over appropriate statin treatment. *See supra* ¶¶ 931.

1007. Moreover, a person of ordinary skill would not have expected that 4 g/day high purity EPA would provide any benefit in terms of stroke or cardiac death prevention in view of JELIS, as JELIS reported no benefits in terms of stroke or sudden cardiac death with EPA. *See supra* ¶¶ 936–39. Yet, in REDUCE-IT, that is what VASCEPA® surprisingly demonstrated, showing significant risk reduction in stroke, cardiovascular death, as well as consistent benefit across all secondary endpoints. *See supra* ¶ 178; PX 272 at 000010, Bhatt NEJM 2019 at AMRN-PEXP-0000698.

1008. A person of ordinary skill in the art in March 2008, moreover, would have found it particularly unexpected that 4 g/day high purity EPA would provide cardiovascular benefits in persons with severe hypertriglyceridemia, given the expectation that purified EPA would produce large increases in LDL-C in persons with very high triglycerides that would nullify any potential cardiovascular benefits in persons with lower triglyceride levels. *See supra* ¶¶ 765–67, 804–06. Those concerns would have been amplified by the use of 4 g/day dose—which was more than twice the EPA dose in JELIS. While in March 2008 a person of ordinary skill would not have understood how the difference in dose would affect cardiovascular outcomes, that person would have been concerned that higher doses might result in adverse lipid effects that could further interfere with any potential cardiovascular benefits. *See supra* ¶¶ 804–06. As shown in MARINE, however, there was no such increase in LDL-C in patients with very high

triglycerides. And in granting the supplemental indication for cardiovascular risk reduction in patients with elevated cardiovascular risk, including in persons with very high TGs, FDA has recognized that REDUCE-IT did establish such a benefit in that population.

1009. This unexpected reduction in cardiovascular risk over and above appropriate statin therapy is a tremendous benefit to patients at risk of cardiovascular disease, including patients with very high triglycerides. Triglycerides are a risk factor for cardiovascular disease, and that risk increases with increasing triglyceride levels. *See* PX 834 at 000001, Christian et al., *Determining Triglyceride Reductions Needed for Clinical Impact in Severe Hypertriglyceridemia*, 127 Am. J. Med. 36 (2014) at AMRN00872270. While patients with elevated triglycerides often take statins in addition to TG-lowering agents to help address that risk, considerable residual cardiovascular risk remains. *See* PX 882 at 000022, Kones, *Primary prevention of coronary heart disease: integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey*, 5 Drug Design Development Therapy 325, 345 (2011) at AMRN-PEXP-0001560 (noting that residual risk in major statin trials is 65 to 75%); PX 272 at 000001, Bhatt NEJM 2019 at AMRN-PEXP-0000689. REDUCE-IT revealed that VASCEPA® dramatically lowers that residual risk, and therefore opens up an entirely new avenue of prevention. Indeed, for patients with very high triglyceride levels, VASCEPA® not only is presumed to reduce risk of pancreatitis, the primary objective for such patients, but also allows patients to benefit from cardiovascular risk reduction.

1010. Further unexpected is that VASCEPA®, a composition of highly purified EPA and substantially no DHA, would contrast so dramatically in its ability to reduce cardiovascular risk in comparison to omega-3 fatty acid preparations containing a mixture of DHA and EPA—the latter of which have consistently failed to demonstrate a significant cardiovascular benefit. At no point prior to publication of the REDUCE-IT results was it appreciated that an omega-3 product containing at least 96% EPA and substantially no DHA, such as VASCEPA®, would so dramatically outperform a DHA/EPA mixture in terms of reduction in cardiovascular risk. Indeed, even in early 2018, just prior to the announcement of REDUCE-IT, publications

continued to group purified EPA with DHA/EPA mixtures when concluding that there was no support for use of omega-3 fatty acids in preventing cardiovascular events. *See, e.g.*, PX 954 at 000001, Aung at AMRN03164724 (concluding on the basis of a meta-analysis that "omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events" and that there was "no support for current recommendations for the use of such supplements in people with a history of coronary heart disease."); PX 953 at 000066, Abdelhamid at AMRN03164036 (concluding on the basis of a meta-analysis that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little."). It never occurred to commentators that purified EPA may have special properties that mixtures of EPA and DHA do not have when it comes to reducing cardiovascular risk, thus prompting commentators to continue to group these together.

E. Industry Praise

1011. The skepticism noted above has been followed with industry praise for VASCEPA®. Industry praise and recognition, especially following initial skepticism, is evidence that an invention was not obvious.

1012. VASCEPA®'s ability to lower TGs in individuals with very high TG levels without increasing LDL-C had been recognized as a "real advance in the treatment of elevated triglycerides" "because it gives you all the benefit without the downside." PX 425 at 000002, O'Riordan, Omega-3 Fatty Acids Fail to Reduce CVD Events in Diabetic Patients: ASCEND, tctMD (Aug. 26, 2018) at AMRN-PEXP-0009484. Lowering TGs in patients with very high TG levels has benefits addresses the risk of TG-induced pancreatitis. The ability to achieve these effects without confounding or complicating attempts to reduce cardiovascular risk is an important advance in lipid-lowering medication, which has been widely recognized. *See, e.g*, PX 441 at 000007, Tajuddin et al., *Prescription omega-3 fatty acid products: considerations for patients with diabetes mellitus*, 2016 Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 109 at AMRN-PEXP-0001814 ("The EPA-only formulation offers an option that is

effective but does not complicate management: while products containing both EPA and DHA may raise LDL-C, the EPA-only product, icosapent ethyl, does not."); PX 852 at 000005, Fialkow, *Omega-3 Fatty Acid Formulations in Cardiovascular Disease: Dietary Supplements Are Not Substitutes for Prescription Products*, 16 Am J Cardiovas Drugs 229 (2016) at AMRN03146091 ("Use of products containing both DHA and EPA also require periodic monitoring of LDL-C during therapy due to the potential for increases in this lipid parameter, while treatment with the EPA-only product, icosapent ethyl has no LDL-C monitoring requirement."); PX 866 at 000002, Castaldo, *Switching statin-treated patients from fenofibrate to the prescription omega-3 therapy icosapent ethyl: a retrospective case series*, 32 Drugs Ther. Perspect. 162, 167 (2016) at AMRN-PEXP-0001209 ("Switching statin add-on therapy from fibrate to icosapent ethyl [VASCEPA®] maintained or improved the lipid profile and was well tolerated with no adverse reactions in a series of patients with hypertension and high cardiovascular risk. Important differences between icosapent ethyl and other add-on therapy options include its good safety and tolerability profile and the fact that it does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label."); PX 843 at 000001-02, 000008, Hassan et al., *Retrospective Case Series of Patients with Diabetes or Prediabetes Who Were Switched from Omega3-Acid Ethyl Esters to Icosapent Ethyl*, 4 Cardiol. Ther. 83 (2015) at AMRN01237873–74, AMRN01237880 ("Notably, OM3FA formulations that contain DHA have been associated with increases in LDL-C, but EPA does not increase LDL-C . . . . Our findings are novel in that we examined the effects of switching from [LOVAZA®] to [VASCEPA®] in patients with diabetes or prediabetes, an important patient population with respect to CVD risk . . . . The results of this analysis support switching such patients from [LOVAZA®] to [VASCEPA®], including those receiving statin treatment . . . . In most patients with prediabetes or diabetes who switched from [LOVAZA®] to [VASCEPA®], LDL-C and other lipid parameters improved.").

1013. Praise and industry appreciation for VASCEPA® have only grown since the results of REDUCE-IT were released in late 2018. Following publication of the REDUCE-IT

findings, doctors and other commentators have recognized that VASCEPA® has (1) succeeded where numerous others failed; (2) upended skepticism about whether an omega-3 product or other TG-lowering product could provide a meaningful reduction in cardiovascular risk; and (3) provided a breakthrough in cardiovascular medicine that will positively affect numerous lives through a cost-effective, well-tolerated medication that lowers triglycerides, avoids substantial LDL-C increases, and substantially lowers cardiovascular risk over and above the cardiovascular risk reduction provided by statins:

- Kastelein et al., *FISHing for the Miracle of Eicosapentaenoic Acid*, N. Engl. J. Med. (2018) at AMRN03168528–29 ("We welcome these results with surprise, speculation, and hope…after a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events.") (PX 959 at 000001–02)

- Neale, *REDUCE-IT: Prescription Fish Oil Prevents CV Events in Patients With High Triglycerides*, tctMD (Nov. 10, 2018) at AMRN03163964 (the results of REDUCE-IT "highlight a new treatment to reduce the residual CV risk seen in patients treated with statins and other types of medications, with a relative risk reduction similar to what has been seen in statin trials") (PX 859 at 000002)

- Fidler, *Amarin Soars as Fish Oil Pill Cuts Risk of Strokes in Long-Awaited Study*, Xconomy (Sept. 24, 2018) at AMRN-PEXP-0001387 ("Indeed, [Dr.] Lepor says the REDUCE-IT results confirm that Vascepa has 'unique characteristics that will not allow me to extrapolate the results from this trial' to other prescribed or over-the-counter fish oils. Lepor now plans to use the Amarin drug in his patients on statins with controlled cholesterol but high triglyceride levels and a history of heart problems or diabetes.") (PX 875 at 000003)

- O'Connor, *Fish Oil Drug May Prevent Heart Attack and Strokes in High-Risk Patients*, The New York Times (Sept. 25, 2018) at AMRN03163962 ("The amount of people around the world who have atherosclerotic disease or diabetes who take a statin and still have elevated triglycerides is enormous," he said. "This has huge implications.") (PX 952 at 000003)

- Feuerstein, *Amarin's stock soars after its fish oil capsule was found to dramatically reduce cardiovascular risks*, STAT News (Sept. 24, 2018) at AMRN03163953 ("In a stunning clinical trial result that upends years of skepticism about the long-term heart benefit of products containing omega-3 fatty acids, Amarin's Vascepa significantly reduced the risk of deaths, heart attacks, strokes, and other serious cardiovascular events compared to a placebo.") (PX 951 at 000001)

- Gingerich, *Icosapent Ethyl Reduces Cardiovascular Death Risk 20% in REDUCE-IT Trial*, MD Magazine (Nov. 11, 2018) at AMRN-PEXP-0007480 (quoting *Michael Miller, MD: REDUCE-IT Trial*, YouTube (Nov. 2018)) **(**"[T]his study is a home run, because it shows for the first time that people with high risk—these are people with high triglycerides, diabetes, metabolic syndrome, and other risk factors—have a big-time event [reduction] on top of a statin and reducing risk [of cardiovascular death]" with use of VASCEPA®) (PX 715 at 000003)

- Hackett, *'Phenomenal' REDUCE-IT establishes triglyceride theory*, CHEST Physician (Nov. 20, 2018) at AMRN-PEXP-0007329 (quoting Prakash C. Deedwania, MD, MDedge (2018)) ("REDUCE-IT is a phenomenal trial and a game changer because it has shown for the first time that triglyceride reduction with an appropriate therapy – in this case icosapent ethyl – when used in appropriate doses can make a significant difference. That's according to Prakash C. Deedwania, MD, chief of the cardiology division at the Veterans Affairs Medical Center/University of California San Francisco Program in Fresno, who joined MDedge reporter Richard Mark Kirkner for a video interview at the American Heart Association scientific sessions.") (PX 902 at 000001)

- JEFFRIES LLC Key Opinion Leaders Conference Call, December 20, 2018, at AMRN-PEXP-0007347 (statement of Dr. Michael Shapiro) ("So I think most people in this field would look at this as a home run. And really view this as being an inflection point in our ability to manage (atherosclerotic) cardiovascular disease. We have a new option that impacts cardiovascular outcomes to a greater extent than just throwing on more LDL cholesterol lowering drugs. . . . So now we have a new option for patients in this category who also happen to have elevated triglycerides where you're going to get more bang for your buck by using kind of a[n] orthogonal therapy.") (PX 714 at 000010)

1014. The industry recognition and praise for VASCEPA® is linked to the Asserted Claims, as patients with TG levels exceeding 500 mg/dl will benefit from the cardiovascular risk reduction and other benefits provided by VASCEPA®, a 4g highly purified EPA treatment with substantially no DHA that lowers TGs and apoB, without substantially raising LDL-C, whether or not they are on a statin. *See supra* ¶¶ 962–74.

F. Commercial Success

1015. The commercial success of a drug whose use according to the instructions in the drug's prescribing information embodies the patented invention can provide objective evidence of the non-obviousness of the patented invention. Economic principles also predict that an invention that has commercial value will be developed, so if companies forego the opportunity to

bring a commercially successful invention to market, the invention must not have been obvious. There must be some causal relation or "nexus" between an invention and commercial success of a product embodying that invention for the evidence of commercial success to be probative of whether the invention was non-obvious.

1016. VASCEPA®'s sales have grown substantially since its launch in January 2013. Net sales account for payment discounts, returns provisions, co-pay mitigation rebates, Medicaid adjustments and government chargebacks, Medicare Part D rebates, commercial rebates, and wholesaler distribution service fees, all of which are included in gross sales but do not form part of net sales. Net sales grew from $26 million for the initial year after launch to $228 million for the sixth year after launch, at a compound annual rate of 54 percent. PX 589, *VASCEPA® Historical Revenue* (Q1 2013–Q4 2018). VASCEPA® has generated $699 million in net sales in its first six years after launch. *Id.*

1017. The trends in prescriptions for VASCEPA® have been similar to trends in sales. In its first year of launch (2013), the number of VASCEPA® prescriptions was approximately 174,000. PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018). By 2018, the number of VASCEPA® prescriptions reached 1.3 million. PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). The number of new prescriptions has similarly grown from approximately 94,000 in 2013 to 530,000 in 2018. PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018); PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). The compound annual growth rate between 2013 and 2018 was 50 percent for total prescriptions and 41 percent for new prescriptions. PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018); PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). In January 2019, total and new prescriptions were 36 percent and 55 percent greater than in January 2018, respectively. PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). The growth in VASCEPA®'s total and new prescriptions are indications of VASCEPA® commercial success.

1018. The growth in the number of total and new prescriptions of VASCEPA® in comparison to competitor molecules, all of which have experienced generic entry, is an indication of its commercial success. From 2013 to 2018, prescriptions for VASCEPA® increased substantially while prescriptions for other omega-3-acid ethyl ester (LOVAZA® and generic LOVAZA®) have been falling. PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018); PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). Prescriptions for VASCEPA® have been also increasing compared to all TG-reducing drugs (fenofibrate, fenofibric acid, gemfibrozil, omega-3-acid ethyl ester, and niacin). PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018); PX 659, IQVIA, *National Prescription Audit* (Feb. 2013–Jan. 2019). The fact that VASCEPA® has gained prescriptions over time despite the availability of generic drugs in its therapeutic category is an indication of the benefits of the innovations embodied in the use of VASCEPA® according to its prescribing information and evidence of its commercial success.

1019. The strong performance of VASCEPA® will continue in the future. Press sources and industry analysts note that the results of the REDUCE-IT trial are likely to have a substantial positive impact on future sales because the trial distinguishes VASCEPA® from therapeutic alternatives that do not have proven cardiovascular benefits. PX 650, Boris et al., *REDUCE-IT CV Outcomes Trial Generates Paradigm Shifting 25% CV Risk Reduction*, SunTrust Robinson Humphrey (Sept. 24, 2018); PX 653, Song & Yee, *Amarin Corporation (AMRN) Stock Has Room to Move Higher, Vascepa Potential SoC—Raising PT to $15*, Jefferies Research Services (Sept. 24, 2018); PX 951, Adam Feuerstein, *Amarin Fish Oil Capsule Shows Dramatic Benefit for Cardiovascular Patients, Potentially Upending Market*, STAT (Sept. 24, 2018); PX 656, Fein et al., *Embracing a Decidedly Non-Orphan Disease Company; Reit Buy and Raising PT to $51*, H.C. Wainwright & Co. (Nov. 12, 2018). Analysts project that VASCEPA® sales will reach $350–$385 million by 2019, and will reach $705 million to $1.7 billion by 2022. PX 657, Beatty & Egan, *Amarin Corp (AMRN) 2019 Revenue Guidance Lower Than Expectations, TP $20 (-$8)*, Citi Research Equities (Jan. 7, 2019); PX 658, Fein et al., *Expect the Continued Underlying*

Vascepa Demand to Drive Value; Reit Buy and $51 PT, H.C. Wainwright & Co. (Feb. 28, 2019); PX 661, Yee et al., *Easy and Great Tuck-In for Pharma Global Salesforce*, Jefferies Research Services (Feb. 27, 2019); PX 663, Boris & Verma, *Lowering Sales on Slower Ramp & Execution Risk; Keener Focus on Shareholder Value Needed*, SunTrust Robinson Humphrey (Jan. 6, 2019); PX 711, Chen et al., *If You Had Any Concerns Going Into 2019, REDUCE-IT*, Cantor Fitzgerald (Feb. 27, 2019). Amarin has also released a forecast for 2019, with net total revenue projected to increase to $350 million, primarily from sales of VASCEPA®. PX 669, Amarin, *Amarin Provides Preliminary 2018 Results and 2019 Outlook*, Globe Newswire (Jan. 4, 2019); PX 716, Amarin, Amarin Reports Record Fourth Quarter and Full Year 2018 Financial Results and Provides Update on Operations (Feb. 27, 2019).

1020. With future expanding sales and lower R&D expenditures following the conclusion of the REDUCE-IT trial, industry analysts are forecasting positive operating income starting around 2019. Specifically, Cantor, Citi, H. C. Wainwright, Jefferies, and SunTrust all expect Amarin to begin generating profits by 2020. PX 657, Beatty & Egan, (Jan. 7, 2019); PX 658, Fein et al., (Feb. 28, 2019); PX 661, Yee et al., (Feb. 27, 2019); PX 663, Boris & Verma, (Jan. 6, 2019); PX 711, Chen et al., (Feb. 27, 2019). Across the three reports with projections for 2022, estimated profits range from approximately $210 million to $892 million in 2022, an average profit of $504 million across the three projections. PX 658 Fein et al., (Feb. 28, 2019); PX 663, Boris & Verma, (Jan. 6, 2019); PX 711, Chen et al., (Feb. 27, 1019).

1021. In the absence of premature generic entry, the revenue Amarin has already earned and is expected to earn on the development and sales of VASCEPA® will cover the costs of R&D, manufacturing, and selling the drug, and will generate positive profits over the course of VASCEPA®'s life cycle. Over its life cycle, VASCEPA® is expected to generate profits in excess of a similar investment in the pharmaceutical industry, *i.e.*, in excess of the returns an Amarin investor could expect to make by holding a diversified pharmaceutical stock portfolio. A break- even point indicates commercial success because it is the point at which a product has recouped all of its costs, and is generating economic profits for its investors. From the break-

even point on, any profits that the product is generating are profits in excess of the typical investment in that industry.

1022. The net present value model ("NPV") is a common method that businesses use to make decisions regarding whether or not to develop a product, and to evaluate its commercial success. The standard approach for such estimation, used by both academics and industry practitioners, is the discounted cash flow ("DCF") approach. PX 602 at 000005–07, Brealey & Myers, *Principles of Corporate Finance* 11–13 (5th ed. 1996) at AMRN-PEXP-0002283–85; PX 616 at 000005–06, Hartmann & Hassan, *Application of Real Options Analysis for Pharmaceutical R&D Project Valuation—Empirical Results from a Survey*, 35 Res. Pol'y 343, 347–48 (2006) at AMRN-PEXP-0002619–20. The DCF approach is used to calculate the NPV of a pharmaceutical product, where the NPV represents the value (calculated at a given point in time) of expected cash flows over a forecast period. The value is calculated relative to the expected value of a similar investment project and, as described above, represents the "additional" profit versus a similar project. These expected cash flows are calculated using both accrued and forecasted costs and revenues.

1023. Relying on five industry analyst projections made between January 6, 2019 and February 28, 2019, PX 657, Beatty & Egan, (Jan. 7, 2019); PX 658, Fein et al., (Feb. 28, 2019); PX 661, Yee et al., (Feb. 27, 2019); PX 663, Boris & Verma, (Jan. 6, 2019); PX 711, Chen et al., (Feb. 27, 2019), and the actual values between 2008 and 2018, PX 590, Amarin Quarterly Financial Summary (Q1 2013–Q4 2018); PX 632, Amarin, *SEC Form 10-K for Fiscal Year Ended December 31, 2012* (Feb. 28, 2013), the consensus estimate of VASCEPA®'s net present value is $1.9 billion under the following assumptions:

- To calculate the net present value of VASCEPA®'s cash flows, the costs and profits associated with VASCEPA® are discounted using a nominal discount rate of 8.6 percent. This rate is based on the estimated cost of capital in the pharmaceutical industry used in the literature for similar analyses. PX 664 at 000021, Scott Harrington, *Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms, in* The Oxford Handbook of the Economics of the Biopharmaceutical Industry 75, 93 (Patricia Danzon & Sean Nicholson eds. 2012). This rate represents the (nominal) rate of return that investors in a

pharmaceutical company such as Amarin would expect to receive from their investment. Therefore, discounting VASCEPA®'s cash flows at this rate estimates the "additional" profit that VASCEPA® can expect to generate relative to similar investment opportunities available to Amarin's investors.

- A generic entry is expected in August 2029 based on the settlement agreement between Amarin and Teva. PX 677, Amarin, *Amarin Announces Patent Litigation Settlement Agreement with Teva* (May 24, 2018).

- The projections made by each analyst are extended to 2029 by applying the annual dollar change in sales in the final year of each analyst's projection to subsequent time periods. This approach is conservative because the expected growth rate of VASCEPA® sales falls over time.

- The final year of sales are prorated to account for potential generic entry in August 2029, when Teva may launch a generic equivalent, at which time Amarin's sales of VASCEPA® is assumed to fall to zero, a conservative assumption.

- The ratio of costs to net sales, or inversely the profit margin, will remain at their level in the last year of each analyst's projections. This approach is conservative given the downward trend in the ratio of costs to net sales in each of these analyst projections, it is likely that costs will continue to fall relative to sales.

1024. The year by which VASCEPA® is predicted to break even (*i.e.*, the cumulative net present value of revenues is sufficient to cover the cumulative net present value of all costs) is 2024, or in its 12th year on the market. Both the net present value and the number of years to break even for VASCEPA® compare favorably to what is typical in the pharmaceutical industry, as discussed in the academic literature. PX 600 at 000006, Berndt et al., *Decline in Economic Returns from New Drugs Raises Questions About Sustaining Innovations*, 34 Health Affairs 245, 250 (2015) at AMRN-PEXP-0002269; PX 612 at 000006, Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, Nature Reviews Drug Discovery 1, 6 (2008) at AMRN-PEXP-0002544; PX 615 at 000012, Grabowski et al., *Returns on Research and Development for 1990s New Drug Introductions*, 20 Pharmacoeconomics 11, 22 (2002) at AMRN-PEXP-0002607.

1025. Another indication that VASCEPA® is a commercial success is its favorable placement in health plan formularies. Coverage of VASCEPA® is high among commercial and

Medicare plans. As of March 2019, 81 percent of commercial plans cover VASCEPA®, and 54 percent of commercial plans have VASCEPA® as a preferred drug. PX 718, Decision Resources Group, *Fingertip Formulary* (Mar. 1, 2019). For Medicare plans, coverage is at 95 percent, while 18 percent of plans have the drug as preferred. *Id.* Medicaid coverage is lower, at 42 percent, with 6 percent of plans including VASCEPA® as a preferred drug. *Id.* For plans offered in the healthcare exchanges, 62 percent and 21 percent of plans have Vascepa® as a covered and preferred drug, respectively, as of March 2019. *Id.*

1026. VASCEPA®'s formulary coverage is favorable when compared to that of other branded drugs used to lower TGs, notably LOVAZA®, TRICOR®, TRILIPIX®, and LOPID®, all of which have generic equivalents available on the market. *Id.* Unsurprisingly, formulary coverage for VASCEPA® is less favorable than that of generic drugs used to lower TG levels. *Id.* However, VASCEPA®'s overall favorable formulary coverage suggests a therapeutic improvement over LOVAZA® and fenofibrate: if VASCEPA® did not offer an improvement over these therapeutic alternatives, insurers would not place VASCEPA® favorably on their formularies at all given the availability of generic alternatives. Thus, VASCEPA®'s favorable formulary status is an indication of its therapeutic benefits.

1027. There is no evidence to indicate that the commercial success of VASCEPA® was driven by excessive marketing efforts. Companies typically vary the amount of marketing support devoted to a product over that product's life cycle. Marketing expenditures during the first few years are usually large relative to sales. Marketing expenditures have been found, on average, to equal 100 percent of sales in a drug's first year, 50 percent in its second year, and 25 percent in its third year. PX 615 at 000008, Grabowski et al. at 18 (2002). Such advertising may be necessary in order to inform physicians and patients about a new drug's characteristics and, for many new drugs, such information would likely diffuse much more slowly without marketing expenditures, resulting in a slower initial growth in sales. In addition, studies demonstrate that marketing expenditures are higher for late entrants in a category, because they need to overcome the brand loyalty established by earlier entrants. PX 598 at 000013, Ernst Berndt, *The U.S.*

Pharmaceutical Industry: Why Major Growth In Times Of Cost Containment?, 20 Health Affairs 100, 112 (2001) at AMRN-PEXP-0002194. After the first few years on the market, marketing expenses relative to sales usually decrease.

1028. The ratio of VASCEPA®'s marketing expenditures to sales for the period 2013 to 2018 was 95 percent in its first year after launch, decreased to 29 percent in its second year, and to 17 percent in its third year. PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018). These numbers are lower than the industry averages reported in the academic literature cited above using the same data source (IMS at the time of the study, now called IQVIA).

1029. Consistent with industry standards, VASCEPA®'s marketing expenditures have declined since the first three years. *Id.* When VASCEPA®'s marketing-to-sales ratios are compared by year since launch with LOVAZA®, yearly marketing-to-sales ratios for VASCEPA® are in line with LOVAZA®'s and are, in fact, lower in several years. PX 642, IQVIA, *Total Promotional Dollar Audit* (Sept. 2005–Dec. 2012); PX 643, IQVIA, *National Sales Perspective Audit* (Sept. 2005–Dec. 2012); PX 645, IQVIA, *National Sales Perspective Audit* (Dec. 2012–Nov. 2018); PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018). For instance, in the second year after launch, LOVAZA®'s marketing-to-sales ratio was approximately 45 percent while VASCEPA®'s was close to 30 percent. PX 642, IQVIA, *Total Promotional Dollar Audit* (Sept. 2005–Dec. 2012); PX 643, IQVIA, *National Sales Perspective Audit* (Sept. 2005–Dec. 2012); PX 645, IQVIA, *National Sales Perspective Audit* (Dec. 2012–Nov. 2018); PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018). Moreover, VASCEPA®'s total marketing expenditures are substantially lower than LOVAZA®'s throughout the first six years after launch. PX 642, IQVIA, *Total Promotional Dollar Audit* (Sept. 2005–Dec. 2012); PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018). In the first full year after launch, IQVIA reported that Amarin spent approximately $33 million in marketing expenditures on VASCEPA®. PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018). In contrast, IQVIA reported that LOVAZA®'s marketing expenditures totaled nearly $86 million in its first full year after launch.

PX 642, IQVIA, *Total Promotional Dollar Audit* (Sept. 2005–Dec. 2012). Annual marketing expenditures for VASCEPA® increased gradually in the subsequent years, but never exceeded $45 million. PX 647, IQVIA, *Total Promotional Dollar Audit* (May 2012–Apr. 2018).

1030. Amarin's marketing messages for VASCEPA® conveyed the patented features of the product. Amarin's website for VASCEPA® and consumer advertising described VASCEPA®'s clinical effectiveness in reducing TGs in patients with severe TG levels and its ability to do so without raising LDL-C. PX 719, Amarin, *VASCEPA® Webpage*, available at https://www.vascepa.com (last visited Mar. 6, 2019). Furthermore, internal documents show that Amarin's direct to consumer communication strategy with respect to VASCEPA® and marketing to healthcare providers emphasized VASCEPA®'s patented features. *See, e.g.*, PX 579, Amarin, *Vascepa DTC Launch* (Nov. 29, 2017). Internal Amarin documents indicate that VASCEPA®'s efficacy in reducing TG levels without increasing LDL-C levels is important to physicians when prescribing VASCEPA®. *See, e.g.*, PX 576 at 000054, Amarin, *VASCEPA 2017 Operating Plan* (2017) at AMRN03151506; PX 577 at 000002, 000010, 000042, AplusA, *VASCEPA® US Market Surveillance Study (ATU)—Wave 2, Final Report of Findings* (Apr. 2017) at AMRN03151517, AMRN03151525, AMRN03151557; PX 580 at 000028–29, ZS Associates, Vascepa Wave 2 PhysPulse Findings (Aug. 19, 2014) at AMRN03151853–54; PX 581 at 000002, 000008, AplusA, *VASCEPA® (Icosapent Ethyl), US Market Surveillance Study (ATU), Final Report of Findings* (Jan. 2016) at AMRN03151939, AMRN03151945; PX 582 at 000004, 000013, 000027, 000037, PharmaSight Research, *VASCEPA® New Campaign Message Convergence Exploration: Healthcare Practitioners and Sales Professionals Representatives* (May 2015) at AMRN03152051, AMRN03152060, AMRN03152074, AMRN03152084; PX 583 at 000006, GfK, *VASCEPA SFE Q3 2017 Quantitative Research, Final Report Prepared for Amarin* (Sept. 2017) at AMRN03152284; PX 585 at 000001–06, Amarin, *Marketing Update* (Dec. 5, 2017) at AMRN03159866–71; PX 586 at 000001–06, Amarin, *Marketing Update, January POAs, 2018* (Jan. 2018) at AMRN03159988–93.

1031. The commercial success of VASCEPA® is not driven by its relatively low price. Instead, VASCEPA® has experienced strong sales growth despite its relatively high price when compared to generic LOVAZA®. The average price per prescription of VASCEPA®, LOVAZA® and generic LOVAZA®, from the IQVIA data shows that, while VASCEPA®'s price has risen steadily since launch, the price of generic LOVAZA® has fallen from an initially similar price to less than a quarter of the price of VASCEPA® in 2018. PX 644, IQVIA, *National Prescription Audit* (Dec. 2012–Nov. 2018); PX 645, IQVIA, *National Sales Perspective Audit* (Dec. 2012–Nov. 2018). Internal Amarin documents also confirm that VASCEPA® is priced competitively when compared to generic LOVAZA®. PX 578, Amarin, *Omega 3 Pricing History* (2008–2016).

1032. Sales of VASCEPA® to patients with high TG levels should be included in an evaluation of whether VASCEPA® is a commercially successful product. Given that LOVAZA® was being prescribed to patients with TG levels below 500 mg/dL at the time of the patented invention (around 2008), PX 641, IQVIA, *National Disease and Therapeutic Index* (Jan. 2008–Nov. 2012), a pharmaceutical company considering whether to develop VASCEPA® would have realized that obtaining approval for VASCEPA® to treat very high TG levels would also give healthcare providers the option, in exercise of their medical judgement, to prescribe VASCEPA® for patients with lower TG levels. In other words, had the Asserted Patents been obvious, other pharmaceutical companies would have been induced by the potential for considerable sales to patients with very high and high TG levels to bring an equivalent drug to VASCEPA® to market sooner.

1033. In addition, the patented invention, and FDA's approval of the patented uses of VASCEPA®, have allowed Amarin to conduct the REDUCE-IT trial to demonstrate that VASCEPA® reduces the risk of cardiovascular disease. Cardiovascular outcome trials require monitoring thousands of patients for years and are expensive to conduct. More than 8,000 patients participated in the REDUCE-IT trial for approximately 5 years. Given the high cost of conducting a cardiovascular outcome clinical trial, Amarin would not have been able to conduct

the trial without the patented invention. Indeed, Amarin's ability to finance the REDUCE-IT trial was dependent on Amarin's ability to demonstrate milestones through success with the MARINE trial and FDA approval. Without the success of VASCEPA® in the very high TG population, investors would have been unwilling to undertake the long drug development process associated with demonstrating a cardiovascular benefit of VASCEPA® in patients with high TG levels. FDA's approval of the patented use of VASCEPA® has allowed Amarin to generate sales to fund the REDUCE-IT trial, resulting in findings in cardiovascular medicine that are likely to have a substantial positive impact on future sales of VASCEPA®.

G. Nexus Between the Objective Indicia of Non-obviousness and the Asserted Claims

1. Use of VASCEPA® according to its product label embodies the Asserted Claims

1034. In the Parties' Joint Stipulated Facts, Defendants stipulated that VASCEPA® will meet the following limitations in the Asserted Claims that describe the pharmaceutical product to be used as the method of treatment claims.

1035. First, Defendants have stipulated that VASCEPA® contains a "pharmaceutical composition," as required by Claims 1 and 16 of the '728 Patent, Claim 14 of the '715 Patent, Claims 1 and 8 of the '677 Patent, Claim 1 of the '652 Patent, and Claims 1 and 5 of the '929 Patent. Joint Stipulated Facts ¶ 204 (ECF No. 324).

1036. Second, Defendants have stipulated that the "pharmaceutical composition" in VASCEPA® comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters," as required by Claims 1 and 16 of the '728 Patent, Claims 1 and 8 of the '677 Patent, and Claim 1 of the '652 Patent. Joint Stipulated Facts ¶ 205 (ECF No. 324).

1037. Third, Defendants have stipulated that VASCEPA® contains a "pharmaceutical composition" "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined," as required by Claim 16 of the '728 Patent. Joint Stipulated Facts ¶ 206 (ECF No. 324).

1038. Fourth, Defendants have stipulated that the "pharmaceutical composition" in VASCEPA® comprises "at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters," as required by Claim 14 of the '715 Patent. Joint Stipulated Facts ¶ 207 (ECF No. 324).

1039. Fifth, Defendants have stipulated that VASCEPA® comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present," as required by Claims 4 and 17 of the '560 Patent. Joint Stipulated Facts ¶ 208 (ECF No. 324).

1040. Sixth, Defendants have stipulated that the "pharmaceutical composition" in a daily dose of VASCEPA® comprises "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids," as required by Claims 1 and 5 of the '929 Patent. Joint Stipulated Facts ¶ 209 (ECF No. 324).

1041. By regulation, Defendants' proposed labeling is copied from VASCEPA®'s label. *See supra* ¶¶ 188–91. The VASCEPA®'s label is thus substantively identical to Defendants' proposed labeling, *see supra* ¶¶ 233–290, and no party nor any expert has suggested that there is any difference between the various labels that would affect the analysis of whether VASCEPA® or Defendants' ANDA Products, or the use thereof, would meet the remaining limitations of the Asserted Claims.

1042. Therefore, for the reasons discussed in ¶¶ 300–653 above, VASCEPA®, and the use of VASCEPA® according to the instructions in VASCEPA®'s labeling, embodies each limitation of the Asserted Claims.

2. There is a nexus between the objective indicia of non-obviousness and the Asserted Claims

1043. There is a nexus, or relationship, between the Asserted Claims and all of the objective indicia of non-obviousness discussed above. First, there is a rebuttable presumption of nexus when objective indicia are tied to a specific product, whose use according to the product label embodies the invention disclosed and claimed in the patent. Use of VASCEPA® according

to its product label embodies the Asserted Claims, and the objective indicia are tied to VASCEPA®, giving rise to a presumption of nexus. *See supra* ¶¶ 1034–42.

1044. Additionally, VASCEPA®'s unexpected results, meeting of a long-felt need (following the failure of others), industry praise (following skepticism), and commercial success, are linked to the features of the Asserted Claims, including the claimed composition (at least about 96% EPA by weight of all fatty acids present and substantially no DHA); its daily dose of 4g/day over a period of 12 weeks or greater; its avoidance of substantial increase in LDL-C in patients with TG levels of at least 500 mg/dl, even in patients not on concomitant lipid altering therapy; its lowering of TGs, and its avoidance of an increase, or reduction in, apoB in individuals having at least 500 mg/dl. *See supra* ¶¶ 962–74, 1014, 1030.

1045. Defendants may contend that there is a lack of nexus between these objective indicia and the Asserted Claims, including the objective indicia relating to the REDUCE-IT trial. None of these arguments has merit.

1046. *First*, Defendants will likely dispute nexus relating to REDUCE-IT because the Asserted Claims are directed to persons with very high triglycerides, whereas REDUCE-IT studied persons with triglyceride levels of less than 500 mg/dl. However, as discussed above, the cardiovascular benefits observed in REDUCE-IT apply to all patients, including those with very high TGs. *See supra* ¶¶ 963–73. Given the results from the MARINE study showing that VASCEPA® does not raise LDL-C in persons with severe hypertriglyceridemia, REDUCE-IT provides a sound basis to conclude that patients with triglyceride levels exceeding 500 mg/dl would benefit from the same risk reduction experienced by subjects in the REDUCE-IT trial. As noted above, REDUCE-IT demonstrated that cardiovascular risk reduction with purified EPA is consistent across different baseline triglyceride levels, including in the upper tertile of patients, which included some patients with baseline TGs of at least 500 mg/dl. *See supra* ¶ 963. Additionally, as noted above, because VASCEPA® lowers below 500 mg/dl the TG levels of many people who initially have very high triglycerides, it at a minimum allows these individuals

to benefit from cardiovascular risk reduction to the same extent as the population studied in REDUCE-IT once their TG levels fall below 500 mg/dl. *See supra* ¶ 967–68.

1047. And moreover, FDA has recognized that the REDUCE-IT results apply to patients with TGs of at least 500 mg/dl. After reviewing the REDUCE-IT results, FDA expanded the approved use of VASCEPA® to include reduction in cardiovascular risk in persons with TG levels over 150 mg/dl, including persons with very high TGs. The inclusion of patients with very high TGs in VASCEPA®'s cardiovascular risk reduction indication demonstrates FDA's view that the REDUCE-IT results apply to individuals with TGs of at least 500 mg/dl. Furthermore, in approving the expanded indication, FDA removed the Limitation of Use that stated, "The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined," thus recognizing VASCEPA®'s cardiovascular benefit in patients with very high TGs. *Compare* PX 940 at 000002, VASCEPA® Prescribing Information (2017) at AMRN03132169, *with* PX 1186 at 000002, VASCEPA® Prescribing Information (2019) at AMRN03174954. *See supra* ¶ 966.

1048. *Second*, Defendants will likely dispute nexus relating to REDUCE-IT because all Asserted Claims cover at least a 12-week course of treatment, while the cardiovascular risk reduction in REDUCE-IT did not manifest until a year or more of treatment. But as the MARINE trial showed, individuals with very high triglycerides taking a daily dose of 4 g of VASCEPA® over twelve weeks experience changes in their biochemistry beyond reductions of triglycerides, including changes in VLDL-C, Lp-PLA2, apoB, and non-HDL as compared to placebo. *See* PX 807 at 000105, MARINE Clinical Study Report at AMRN00053561. The buildup of EPA during this 12-week period provides beneficial physiologic changes to the cardiovascular environment, bringing people closer to the point at which the reduction in cardiovascular risk will manifest in a statistically significant way. While it will take longer than 12 weeks for that reduction to manifest, the way for patients to get this benefit is to start VASCEPA® as soon as possible, as delay in starting only serves to put off the benefits observed in REDUCE-IT. That doctors have switched patients from LOVAZA® to VASCEPA® following

announcement of the results in REDUCE-IT, moreover, underscores the connection between the cardiovascular benefits seen in REDUCE-IT and the method of treatment covered by the Asserted Claims.[34]

1049. *Third*, Defendants will likely dispute nexus between the benefits observed in REDUCE-IT and the asserted claims forbidding concurrent statin use, because all patients in REDUCE-IT were on statins. But REDUCE-IT examined the degree to which VASCEPA® offers a cardiovascular benefit *beyond* appropriate statin therapy, and showed that VASCEPA® in fact offers powerful cardiovascular risk reduction *over and above* the risk reduction provided by statins. Given that VASCEPA® provides this additional cardiovascular benefit *beyond* statin use, patients on VASCEPA® derive significant cardiovascular benefit from VASCEPA®, even if not taking statins—especially since there is no evidence to suggest that EPA depends on statins for its cardiovascular benefit.

XXXVI. REMEDIES

1050. Plaintiffs are entitled to a declaratory judgment that Defendants' making, using, selling, offering to sell, or importing the products described in Defendants' ANDAs, or inducing

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[34] *See, e.g.*, PX 714 at 000005, Jefferies LLC, Cardiovascular Key Opinion Leaders Call Transcript (Dec. 20, 2018) at AMRN-PEXP-0007342 (statement of Dr. James Underberg, president of the National Lipid Association, noting that after REDUCE-IT "I have started asking (aide) are you using any fish oil preparations? Are you using any prescription Omega-3 preparations and if you are then I think we should change that to VASCEPA® at the use dose of four grams a day."); *see also id.* at 000006 ("So in other words I may have a patient who has been taking generic version of what used to be LOVAZA®, who I've suggested based on this data, this fairly specific data, VASCEPA® is appropriate."); PX 712 at 000001, Cantor Fitzgerald, *Company Update, Don't Die Of A Broken Heart; Physician Survey Shows How Vascepa Can Help* (Jan. 30, 2019) at AMRN-PEXP-0007220 (survey revealing that physicians would increase their year over year usage of VASCEPA® and that the REDUCE-IT trial was the key driver for such increase); PX 970 at 000002, Archila et al., *Boston Doc Day 'Lipid Panel' Recap: Room for New Players in the LDL-C Category; Docs Seek Multifocal Approach to Management,* Stifel (Jan. 16, 2019) at AMRN-PEXP-0008691 ("[P]hysician sentiment around the [REDUCE-IT] data is very positive . . . Dr. Mitri was the most bullish on VASCEPA®'s prospects noting elevated triglyceride levels are particularly significant in the diabetic population (the majority of her population she treats) so she expects to increase her writing for VASCEPA® meaningfully.").

such conduct, would constitute infringement of the Asserted Claims. *See, e.g.*, 28 U.S.C. § 2201; 35 U.S.C. § 271(e)(2); *Allergan, Inc. v. Alcon Labs.*, 324 F.3d 1322, 1330 (Fed. Cir. 2003) (§ 271(e)(2) creates an "act of infringement" based upon the filing of an ANDA, which permits the district court to exercise its jurisdiction under 28 U.S.C. § 1338(a)); *Teva Pharm. USA, Inc. v. Novartis Pharm. Corp.*, 482 F.3d 1330, 1342 (Fed. Cir. 2007) (under 35 U.S.C. § 271, filing of an ANDA creates a "controversy" sufficient to confer jurisdiction on the district court over a declaratory judgment action).

1051. Plaintiffs are entitled to a permanent injunction enjoining Defendants and their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliates, and those persons in active concert or participation with any of them, from making, using, selling, offering to sell, or importing their ANDA Products, or inducing any such conduct, until after the expiration of the Asserted Patents, including any extensions and additional periods of exclusivity. *See, e.g.*, 35 U.S.C. § 271(e)(4); 35 U.S.C. § 283.

1052. Plaintiffs are entitled to reasonable attorney fees and costs pursuant to 35 U.S.C. § 285. *See, e.g.*, 35 U.S.C. § 285; 35 U.S.C. § 271(e)(4); *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1756 (2014) ("[A]n 'exceptional' case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) . . . . District courts may determine whether a case is 'exceptional' in the case-by-case exercise of their discretion, considering the totality of the circumstances.").

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on January 6, 2020, I caused true and correct copy of **PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** to be filed with the Clerk of the Court using the Court's CM/ECF system, and service was thereby effected electronically on the following counsel of record in this matter:

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